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# THE AMERICAN REVIEW OF TUBERCULOSIS

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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

## CONTENTS

Chemical Studies on Thiosemicarbazones with Particular Reference to Antituberculous Activity. Robert Behnisch, Fritz Mietzsch, and Hans Schmidt ..... 1

Investigations on the Antituberculous Activity of the Thiosemicarbazones *In Vitro* and *In Vivo*. Gerhard Domagk ..... 8

The Present Status of the Chemotherapy of Tuberculosis with Conteben, a Substance of the Thiosemicarbazone Series. A Review. Anton Mertens, and Rolf Bunge ..... 20

The Implications of Changing Morbidity and Mortality Rates from Tuberculosis. Herbert R. Edwards, and G. J. Drolet ..... 39

Prevalence of Clinically Significant Pulmonary Tuberculosis among Inmates of New York State Penal Institutions. Julius Katz, and Robert E. Plunkett ..... 51

Postoperative Management of Thoracoplasty Patients. John Alexander ..... 57

The Value of Cytological Diagnosis of Pulmonary Malignancy. Louis H. Clerf, and Peter A. Herbut ..... 60

Properties of a Culture of BCG Grown in Liquid Media Containing Tween 80 and the Filtrate of Heated Serum. René J. Dubos, Frank Fenner, and Cynthia Pierce ..... 66

Experimental Pulmonary Tuberculosis in the Dog. Comparison of Lesions in Puppies and in Mature Dogs. Francis D. Gunn, and John J. Sheehy ..... 77

Studies on the Contagiousness of Coccidioidomycosis. II. The Fate of Spherules in Sputum Exposed Out of Doors. Sol Roy Rosenthal, and Francis H. Elmore ..... 95

Studies on the Contagiousness of Coccidioidomycosis. III. Infection in Guinea Pigs by Contact with Diseased Animals. Sol Roy Rosenthal, and Francis H. Elmore ..... 106

Tuberculosis of the Stomach and the Stomach in Tuberculosis: A Review with Particular Reference to Gross Pathology and Gastroscopic Diagnosis. Eddy D. Palmer ..... 116

Case Reports:

Pulmonary Alveolar Adenomatosis. John H. Moyer ..... 131

Miliary Tuberculosis. Report of a Case of Long Duration without Chemotherapy. Harry R. McPhee ..... 138

American Trudeau Society: Report to Clinical Subcommittee on German Experience with Thiosemicarbazone. H. Corwin Hinshaw, and Walsh McDermott ..... 145

Letters to the Editors:

Pulmonary Coccidioidomycosis. H. E. Bass ..... 158

Abstracts ..... 1

## ANNUAL MEETING—WASHINGTON, D. C.
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See page 8

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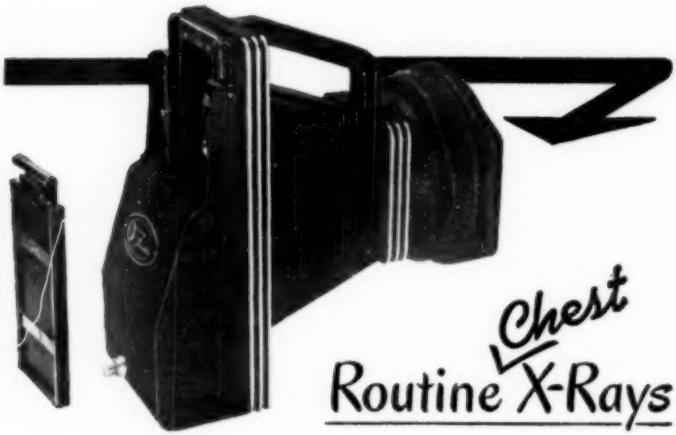


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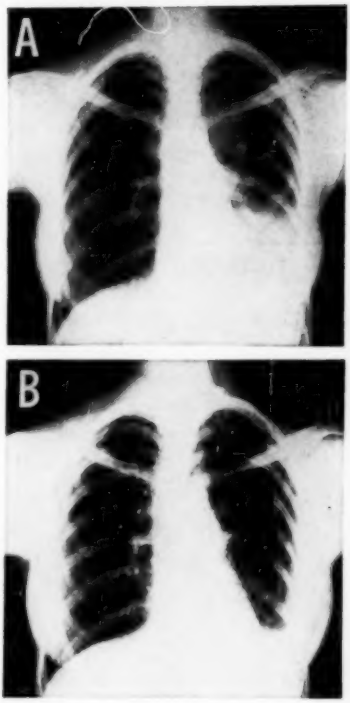


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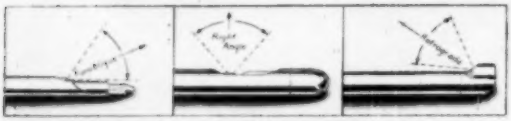

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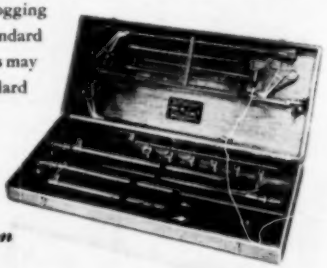

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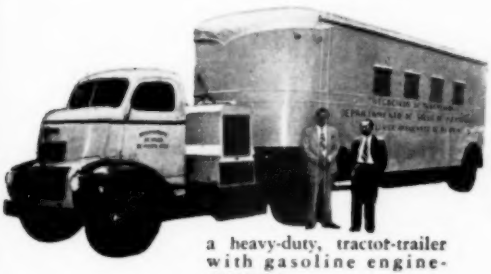

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VOLUME 61 *January 1950* NUMBER 1

# CHEMICAL STUDIES ON THIOSEMICARBAZONES WITH PARTICULAR REFERENCE TO ANTITUBERCULOUS ACTIVITY[1,2]

ROBERT BEHNISCH, FRITZ MIETZSCH, AND HANS SCHMIDT

(Received for publication October 21, 1949)

## INTRODUCTION

Of the multiplicity of substances recommended for the treatment of tuberculosis in man, compounds from three different classes of substances have at present won particular importance: the glucoside streptomycin, belonging to the series of antibiotics, para-aminosalicylic acid, and the thiosemicarbazones, particularly 4-acetylaminobenzaldehyde thiosemicarbazone (Conteben, or TbI/698).

Streptomycin, discovered by Waksman, Schatz, and Bugie (1) and first tested in tuberculosis by Feldman and Hinshaw (2), has been investigated extensively, particularly in the United States. First synthesized in 1889, 4-aminosalicylic acid (3), the activity of which was first observed by Lehmann (4), has been studied in detail, particularly in Sweden and in the United States. The thiosemicarbazones, particularly TbI/698, were developed in Germany in the laboratories of the Farbenfabriken Bayer at the Elberfeld Works by Behnisch, Mietzsch, and Schmidt (5) in cooperative work with Domagk (5). The clinical investigations with these compounds were undertaken by Moncorps, Kalkoff, Kuhlmann, Klee, Heilmeyer, Malluche, and others.

Briefly, the development leading to the thiosemicarbazones took the following course: Through the study of the sulfonamides and sulfones, new hopes were awakened in respect to the chemotherapy of tuberculosis when the sulfones, Promin, Promizole, and Diasone (Feldman), as well as compounds of the sulfathiazole and sulfathiodiazole series (Domagk) showed a limited activity. Later it was found, in compounds which Behnisch gave to Domagk for chemotherapeutic examination, that the development of the activity is not dependent upon the sulfonamide or sulfone groups, nor upon the thiazole or thiodiazole rings,

[1] From the Laboratories of the Farbenfabriken Bayer at the Elberfeld Works, Leverkusen, Germany.

[2] The translation of this article into English was obtained through the courtesy of Schenley Laboratories, Inc., New York, N. Y.

but that an open, chain-like arrangement of the nitrogen and sulfur atoms, such as is present in the thiosemicarbazones represents, when suitably substituted, a much more active basic principle.

## RELATION OF CHEMICAL STRUCTURE TO ANTITUBERCULOUS ACTIVITY

Among the compounds of this type, the condensation products of oxo compounds with thiosemicarbazide, known as thiosemicarbazones, proved to be the most efficacious. The examination of numerous such thiosemicarbazones which we prepared allowed us to recognize certain relationships between substitution and activity. The following points of view were recognized as important to the manifestation and magnitude of the action.

1. The sulfur atom of the thiosemicarbazones plays an essential role. Semicarbazones, oximes, hydrazones, azines, aniles, and other compounds of similar structure are inactive. Moreover, other sulfur-bearing compounds, such, for example, as carbothiohydrazones or dithiocarbazonic acid alkyl esters, closely related to the thiosemicarbazones, are more weakly, or not at all, active.

2. Thiosemicarbazones of aldehydes behave more favorably than do thiosemicarbazones of ketones. The latter are generally less effective and materially more toxic.

3. The aldehyde is advantageously of aromatic nature. Aldehydes of the aliphatic or of the sugar series yield less active thiosemicarbazones.

4. Substitution at the nitrogen atoms of the thiosemicarbazide grouping causes the action to disappear increasingly with the size of the substituents. Even the use of methyl-thiosemicarbazide yields materially less effective thiosemicarbazones.

5. The action can be increased materially, however, by the introduction of suitable substituents on the aromatic ring. The nature and position of these substitutents determine the magnitude of the effectiveness. Particularly those thiosemicarbazones have proved to be advantageous which have been substituted with groups containing nitrogen, oxygen, and sulfur. The following compounds have been investigated and in the discussion below are designated by the appropriate roman numeral:

I. $O_2N \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

II. $H_2N \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

III. $CH_3CONH \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

IV. $C_2H_5CONH \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

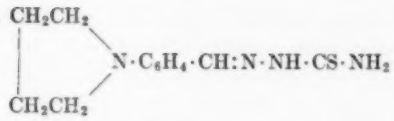
V. $NaOOC \cdot CH_2CH_2CONH \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

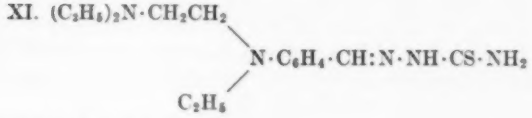
VI. $C_6H_5CONH \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

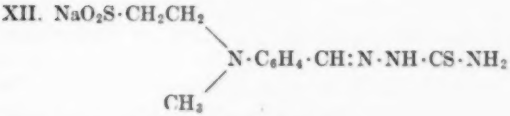
VII. $H_3CO \cdot C_6H_4 \cdot CH{:}N \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

VIII. $C_6H_{11}O_5 \cdot HN \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

IX. $(CH_3)_2N \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

X. 

XI. 

XII. 

XIII. $H_3CO \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XIV. $H_9C_4O \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XV. $CH_3CO \cdot O \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XVI. $(C_2H_5)_2N \cdot CH_2CH_2O \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XVII. $NaOOC \cdot CH_2O \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XVIII. $3\text{—}CH_2N(CH_3)_2\text{-}4\text{-}HO \cdot C_6H_3 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XIX. $3\text{-}(NO_2,NH_2,NHCOCH_3)\text{-}4\text{-}HO \cdot C_6H_3 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XX. $H_3CS \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XXI. $C_2H_5O_2S \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2$

XXII. $H_3CO \cdot C_6H_4 \cdot CH{:}N \cdot NH \cdot CS \cdot NH_2 \rightarrow H_3CO \cdot C_6H_4 \cdot \underset{1}{CH_2} \cdot \underset{2}{NH} \cdot \underset{3}{NH} \cdot \underset{4}{CS} \cdot NH_2$

XXIII. $H_3CO \cdot C_6H_4 \cdot \underset{I}{CH} \cdot \underset{I}{N} \cdot NH \cdot CS \cdot NH_2$

If in the preparation of nitrogen-substituted derivatives we start with nitrobenzaldehydes, then active nitrobenzaldehydes-thiosemicarbazones (I) are obtained. The para position is the most advantageous, with the action decreasing in the order para-meta-ortho. This phenomenon can be observed frequently, but is not the fixed rule. We are familiar with instances in which the meta compounds are just as effective as the para compounds. Reduction of the nitro compounds to amino compounds leads to the materially less effective aminobenzaldehyde-thiosemicarbazones (II), which, however, are important as the starting materials for further substitution products. Acylation leads to the very effective acylaminobenzaldehyde-thiosemicarbazones (III, IV). In the aliphatic series the activity first increases with acylation and then decreases again with higher acyl groupings, for example, stearoyl. Benzoylation (VI) also works out very advantageously. Substituents at the benzoyl grouping have a distinct effect

upon the activity. Reaction of the amino benzaldehyde-thiosemicarbazones with aldehydes leads to very effective azomethine compounds (VII), and with sugars to N-glucosides (VIII). The alkylamino-benzaldehyde-thiosemicarbazones were further recognized as being very effective. They may contain purely aliphatic alkyl groups, such as IX, or the amino-nitrogen may simultaneously also be a member of a heterocylic ring, as X. In this way it is also possible to obtain compounds readily soluble in water if the alkyl grouping contains basic groups (XI) or acid groups (XII) which produce solubility in water (Cf. a similar behavior in the acylamino series in V).

Among the oxygen-substituted derivatives, the free-hydroxyl compounds again are less outstanding in respect to their favorable action than are the alkoxy and acyloxy compounds, such as XIII, XIV, and XV. By the use of basic- or acid-substituted alkoxy groups or by application of Mannich's reaction to the free-hydroxyl compounds, the water-soluble derivatives XVI, XVII, and XVIII may be obtained. The grouping of a hydroxyl in the 4-position and of a nitrogen-bearing grouping in the 3-position, which is obtained in the salvarsan series, did not lead, in the thiosemicarbazone series, to any noteworthy result in any of the cases investigated—XIX (nitro, amino, and acetylamino derivatives).

We also found very effective compounds in the group of the thiosemicarbazones substituted with sulfur-bearing groups. For example, the alkylmercapto compounds (XX) as well as their oxidation products, the alkyl sulfone compounds (XXI), are markedly effective, while the sulfoxide compounds lag behind. In these series we studied particularly accurately the effect of alkyl substitution in a straight line or branched. Finally, mention must also be made of those benzaldehyde-thiosemicarbazones which carry carboxylic acid or carboxylic acid ester groups in the para or meta position and which stand out because of their exceptionally good action. The magnitude of the alcohol serving for the esterification again has important influence upon the magnitude of the effectiveness.

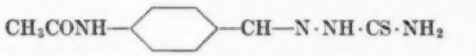
In regard to the action-mechanism, it is probable that the action is primarily attributable to the unsplit thiosemicarbazone or to certain addition products. Cleavage into free aldehyde and free thiosemicarbazide as the effective products is not probable, for the free aldehydes proved to be inactive while the thiosemicarbazide proved to be very toxic and only slightly active. On the other hand, the double bond in the thiosemicarbazones can be hydrogenated as shown in the process indicated in XXII. The 1-benzylthiosemicarbazides thus obtained still possess the full effectiveness, while cleavage to the free thiosemicarbazide is no longer possible. These interesting compounds form neutral soluble salts with mineral acids.

Other interesting compounds are produced by the addition of other atoms or groups of atoms at the azomethine double bond as, for example, in XXIII. Chlorine, bromine, iodine, and thiocyanogen may be added in a simple manner, very effective compounds being thereby obtained. Quite a few facts interesting chemically can thereby be observed, since the addition reaction can, according to the conditions prevailing, lead to different substances whose constitution has in detail not yet been completely clarified. The addition of iodo-alkyl to the sulfur atom also leads to effective compounds.

## CONTEBEN

Of the large number of compounds mentioned, 4-acetylaminobenzaldehyde thiosemicarbazone (TbI/698) has proved to be the most effective preparation, which, after careful pharmacological investigation, has been extensively tested clinically. It has been placed on the market in Germany under the trade name "Conteben."

4-acetylaminobenzaldehyde-thiosemicarbazone, TBI/698 (Schmidt No. 1041X, Conteben)



*Properties:* Conteben is a pale yellow, finely crystalline powder of bitter taste. It has the formula $C_{10}H_{12}ON_4S$, a molecular weight of 236.28, and melts with decomposition at about 230°C. This compound is almost insoluble in water. In 100 cc. of water 0.0088 Gm. dissolves at 20°C., and 0.0172 Gm. at 37°C. The solubility is very dependent upon the pH. Human urine is able to retain a multiple of these quantities in solution. Clinical investigations have indicated that the solubility of the compound in serum is better than in water alone. Conteben is only sparingly soluble in alcohol, acetone, and chloroform, but on warming is soluble in dilute aqueous caustic soda, glycerol, and acetic acid; at room temperature it is even soluble in ethanolic and methanolic caustic soda.

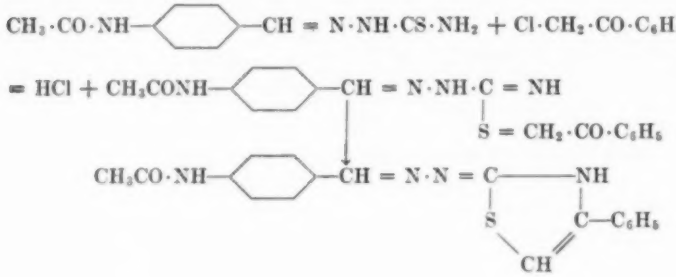
In 2 cc. of 50 per cent sulfuric acid, 0.2 Gm. of Conteben dissolves without warming to a clear light yellow liquid. If 0.1 Gm. of sodium nitrite is added to the solution, the latter then becomes intensely red in color. If 0.1 Gm. of Conteben is dissolved in 5 cc. of dilute caustic soda, and 2 cc. of lead acetate solution are added and the mixture is boiled, the solution becomes dark in color with the separation of black flecks of lead sulfide.

The addition of copper sulfate solution to a solution of Conteben in 50 per cent sulfuric acid precipitates the gray-green copper complex salt. This reaction is extraordinarily sensitive and also indicates small amounts of Conteben by a green coloration. Conteben has proved to be an excellent producer of complex compounds and also yields insoluble complex salts with other heavy metals.

*Determination in body fluids:* The quantitative determination of Conteben in body liquids, for example, in urine, may be made by two different methods. They were developed by Wollenberg in the analytical laboratory of the Elberfeld Works, Farbenfabriken Bayer, who will report thereon in the near future. By boiling the drug for several hours with dilute sulfuric acid, various reactions take place, including the splitting off of the acetyl group. The aromatic amino group thus liberated can be diazotized. By coupling the diazo compound with 1-ethylaminonaphthalene or with 2-oxynaphthalene-3,6-disulfonic acid, red dyes are obtained (as suggested by Hecht's method for the determination of sulfone amides) which can be determined colorimetrically. According to Wollenberg, 1-phenylaminonaphthalene-8-sulfonic acid has proved to be a particularly suitable coupling component. It yields a blue-red dye in acetic acid. Beer's Law (dependence of the extinction upon the concentration) applies strictly

thereto. Furthermore, the formation of the dye is particularly dependent upon the pH of the coupling solution.

While the aromatic half of the molecule is determined by this reaction, the other sulfur-bearing half can be obtained by the second method. By reaction of Conteben with ω-chloroacetophenone, closure of the ring takes place with the formation of a phenylthiazole derivative, analogous to a reaction carried out by Bose (7).



This reaction product is characterized by an intensive yellow coloration, which is suitable for the colorimetric determination and also makes it possible to determine the drug in the urine.

The use of both methods makes it possible to follow the excretion of the drug by measurement after administration of the preparation. While the first method is limited to those thiosemicarbazones in which an aromatic amino group can be liberated by hydrolysis, the second method permits the quantitative determination of all thiosemicarbazones which, like Conteben, contain at least two free hydrogen atoms in the thiosemicarbazide. By the application of the two methods beside each other, it also becomes possible in the case of Conteben to gain information on the question of the cleavage in the organism and the excretion of the cleavage products. In the elementary analytical determination of Conteben and allied substances, consideration must be given to the fact that, as derivatives of hydrazine, they have a tendency to form a nitrogenous carbon which is combustible with difficulty. Consequently, it is necessary to provide for a very energetic combustion in order to obtain correct values. The method of Unterzaucher (8) is preferentially applicable for the determination of the nitrogen.

*Parenteral administration:* In spite of its slight solubility in water, the use of Conteben is not confined to administration by mouth. By means of the addition of solubilizing agents like Antipyrine, it becomes possible to increase the solubility of Conteben so that the preparation may be used for injection therapy. Suitable solutions for injection can also be prepared in glycols, like 1–2 propylene glycol, or acid amides, like formamide and methylacetamide.

In case highly concentrated neutral aqueous solutions of a thiosemicarbazone are required for special therapeutic purposes, then, in place of Conteben, other

compounds of the thiosemicarbazone series must be adapted, the suitability of which for the desired special purpose is still the subject of detailed investigation.

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# INVESTIGATIONS ON THE ANTITUBERCULOUS ACTIVITY OF THE THIOSEMICARBAZONES IN VITRO AND IN VIVO[1,2]

GERHARD DOMAGK

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When the sulfonamides, the first agents with which acute bacterial infections could be combated in man, were discovered, it was obvious that a search would be made for agents effective against tuberculosis. But twenty years have already passed since we began these investigations systematically. In 1940, I reported that a substance which was already known throughout the world, particularly for combating gonorrhea, the well-known sulfathiazole (Eleudron or Cibazole) was active against tubercle bacilli *in vitro*. The sulfathiodiazoles also behaved similarly.

In the test tube these substances exert a specific inhibiting action upon cultures of the tubercle bacillus. Our method was to add definite amounts of the substances to be tested to egg culture media. Eleudron and Globucide showed inhibition in concentrations of 1:25,000 and 1:50,000, respectively, as compared with Debenal and Marfanile at below 1:5,000. During the subsequent pursuit of these observations, it was found that, in order to obtain this inhibiting effect, neither sulfonamide groupings nor the thiazole- or thiodiazole-groupings alone were at all necessary to obtain this effect, because the thiosemicarbazones Tb I synthesized by the chemists Mietzsch, Behnisch, and Schmidt, proved to be still more effective.

Streptomycin and para-aminosalicylic acid (PAS) show similar inhibiting effects. However, a fundamental difference exists in that Eleudron, Globucide, and para-aminosalicylic acid, on the one hand, are strongly hindered in their action by the presence of para-aminobenzoic acid, while the thiosemicarbazones and streptomycin are not.

It is well recognized that such an inhibiting action *in vitro* in itself does not suffice for assuring chemotherapeutic action *in vivo*. Chemotherapeutic substances must not harm leukocytes and histiocytes and, in therapeutically effective doses, they must generally be well tolerated. In animal experiments the thiosemicarbazones are well tolerated, almost as well as sulfathiazole. Para-aminosalicylic acid and streptomycin showed such low toxicity with various species of animals that a chemotherapeutic effect was to be expected. Many other substances, which *in vitro* showed similar inhibition values, have failed to show significant activity *in vivo* or have proved to be too toxic for laboratory animals. Streptomycin and the thiosemicarbazones are among the few substances which possess important *in vivo* activity. The effects of Eleudron and para-aminosalicylic acid can be detected in animal experiments, but are slight.

[1] From the Laboratories of the Farbenfabriken Bayer at the Elberfeld Works, Leverkusen, Germany.

[2] The translation of this article into English was obtained through the courtesy of Schenley Laboratories, Inc., New York, N. Y.

TABLE 1

*Guinea Pig Tuberculosis Experiment of March 9, 1949. Guinea Pigs Infected Subcutaneously with 1 mg. of Tubercle Bacilli of the Human Type in the Flexure of the Groin (left)*

The drugs were administered daily subcutaneously during the period from March 9 to May 19, a total of 50 times

Autopsy on May 31, 1949

| | ANIMAL NO. | WEIGHT | SPLEEN | LIVER | LUNG |
|---|---|---|---|---|---|
| | | Gm. | | | |
| Control | 4401 | 300 | +++ | + | +++ |
| Control | 4402 | 300 | +++ | + | +++ |
| Control | 4403 | 380 | +++ | + | + |
| Control | 4404 | 380 | +++ | + | +++ |
| Tb I | | | | | |
| 50 mg. | 4405 | 300 | ++ | 0 | + |
| 60 mg. | 4406 | 300 | + | + | (+) |
| 70 mg. | 4407 | 300 | + | 0 | + |
| 80 mg. | 4408 | 300 | (+) | 0 | 0 |
| 90 mg. | 4409 | 300 | ? | + | (+)death 30.5 day |
| 100 mg. | 4410 | 300 | 0 | 0 | 0 |
| 110 mg. | 4411 | 300 | 0 | 0 | 0 |
| 120 mg. | 4412 | 300 | 0 | 0 | 0 |
| 130 mg. | 4413 | 300 | 0 | 0 | 0 death 17.4 day |
| 140 mg. | 4414 | 300 | 0 | 0 | 0 death 27.3 day |
| 150 mg. | 4415 | 320 | 0 | 0 | 0 |
| Streptomycin | | | | | |
| 50 mg. | 4416 | 320 | ++ | ? | 0 |
| 60 mg. | 4417 | 320 | ++ | + | 0 |
| 70 mg. | 4418 | 320 | ++ | 0 | 0 |
| 80 mg. | 4419 | 320 | +++ | 0 | 0 |
| 90 mg. | 4420 | 320 | ++ | 0 | 0 |
| 100 mg. | 4421 | 320 | 0 | 0 | 0 |
| 110 mg. | 4422 | 320 | + | 0 | 0 |
| 120 mg. | 4423 | 320 | 0 | 0 | 0 |
| 130 mg. | 4424 | 320 | ? | ? | ? death 3.5 day |
| 140 mg. | 4425 | 320 | + | ? | 0 |
| 150 mg. | 4426 | 320 | + | 0 | 0 |
| *p*-aminosalicylic acid | | | | | |
| 50 mg. | 4427 | 320 | +++ | +++ | +++ |
| 60 mg. | 4428 | 320 | ++ | ? | 0 |
| 70 mg. | 4429 | 320 | ++ | ? | ++death 28.3 day |
| 80 mg. | 4430 | 320 | ++ | ? | ++ |
| 90 mg. | 4431 | 320 | ++ | + | ++ |
| 100 mg. | 4432 | 320 | +++ | ++ | ++death 26.5 day |
| 110 mg. | 4433 | 320 | ++ | 0 | + |
| 120 mg. | 4434 | 320 | + | + | + death 8.5 day |
| 130 mg. | 4435 | 320 | ? | ? | ? death 4.4 day |
| 140 mg. | 4436 | 330 | ? | ? | ? death 21.4 day |
| 150 mg. | 4437 | 330 | +++ | ? | ++ |

Explanation of the symbols: +++ = Marked tuberculous changes in the organs; ++ = Moderate tuberculous changes in the organs; + = Slight tuberculous changes in the organs; 0 = No tuberculous changes in the organs.

## TABLE 2

*Experiment of June 7, 1949 Guinea Pigs Infected Subcutaneously with 1 mg. of Tubercle Bacilli of the Human Type in the Flexure of the Groin*

The drugs were administered 30 times between June 8 and July 19, 1949

Autopsy July 25, 1949

| | ANIMAL NO. | INJECTION SITE | NODE | SPLEEN | LIVER | LUNG |
|---|---|---|---|---|---|---|
| Controls: 6; died spontaneously: 2; autopsied: 4 | | | | | | |
| Controls | 4847 | + | + | + | 0 | + |
| | 4850 | + | + | + | 0 | + |
| | 4959 | + | + | + | 0 | + |
| | 4960 | + | + | + | 0 | + |
| Tb I 50 mg. (S.C.) | 4851 | + | + | 0 | 0 | (+) |
| | 4852 | Died spontaneously, no TB lesions | | | | |
| | 4853 | + | + | 0 | 0 | ? |
| | 4854 | + | + | 0 | ? | ? |
| Tb I 100 mg. (S.C.) | 4855 | Died spontaneously, no TB lesions | | | | |
| | 4856 | + | + | 0 | 0 | 0 |
| | 4857 | + | + | 0 | 0 | 0 |
| | 4858 | + | + | 0 | 0 | 0 |
| Tb I 150 mg. (S.C.) | 4859 | + | 0 | 0 | 0 | 0 |
| | 4860 | + | (0) | 0 | 0 | 0 |
| | 4861 | + | (+) | 0 | 0 | 0 |
| | 4862 | + | (+) | 0 | 0 | 0 |
| PAS 50 mg. | 4863 | Died spontaneously | | +++ | | |
| | 4864 | + | + | + | + | + |
| | 4865 | + | + | + | ? | + |
| | 4866 | + | + | ? | ? | + |
| PAS 100 mg. | 4867 | + | + | ? | ? | ? |
| | 4868 | + | + | + | + | + |
| | 4869 | + | + | ? | + | + |
| | 4870 | Died spontaneously | + | ? | | |
| PAS 150 mg. | 4871 | + | + | + | + | ? |
| | 4872 | Died spontaneously | | +++ | | |
| | 4873 | + | + | + | ? | ? |
| | 4874 | Died spontaneously | | | | |
| Tb I plus PAS 50 mg. | 4911 | Died spontaneously | | | | |
| | 4912 | + | + | 0 | 0 | + |
| | 4913 | + | + | 0 | 0 | ? |
| | 4914 | + | + | 0 | 0 | + |
| 100 mg. | 4915 | Died spontaneously | | | | |
| | 4916 | + | (+) | 0 | 0 | ? |
| | 4917 | + | + | 0 | 0 | 0 |
| | 4918 | Died spontaneously | | | | |
| 150 mg. | 4919 | + | 0 | 0 | 0 | ? |
| | 4920 | + | 0 | 0 | 0 | + |
| | 4921 | + | 0 | 0 | 0 | ? |
| | 4922 | Died spontaneously | | | | |

Explanation of the symbols: + = TB lesions not visible macroscopically; 0 = No TB lesions; ? = No lesions distinct macroscopically, but still detectable microscopically.

## OBSERVATIONS

In table 1 may be seen the results of a comparison of the respective antituberculous activities of 4-acetylaminobenzaldehyde thiosemicarbazone (Tb I), streptomycin, and *p*-aminosalicylic acid in guinea pigs. The details of this

TABLE 3

*Same Experiment as in Table 2, Carried out in the Same Manner with Guinea Pigs Infected Subcutaneously with Tubercle Bacilli of the Bovine Type 1 mg. in the Flexure of the Groin on June 7, 1949*

Up to July 25, 5 of 6 of the control animals had died spontaneously from tuberculosis. Therefore, the last control animal was autopsied on July 25, numerous tuberculous lesions being found in the spleen, liver, and lungs.

| | ANIMAL NO. | AUTOPSY FINDINGS | | | | |
|---|---|---|---|---|---|---|
| | | Injection site | Lymph node | Spleen | Liver | Lung |
| Tb I 50 mg. | 4965 | + | + | 0 | 0 | 0 |
| | 4966 | + | + | 0 | 0 | 0 |
| | 4967 | + | + | 0 | 0 | 0 |
| | 4968 | + | + | 0 | 0 | 0 |
| Tb I 100 mg. | 4969 | + | (+) | 0 | 0 | 0 |
| | 4970 | + | (+) | 0 | 0 | 0 |
| | 4971 | + | (+) | 0 | 0 | 0 |
| | 4972 | + | (+) | 0 | 0 | 0 |
| Tb I 150 mg. | 4973 | + | + | 0 | 0 | 0 |
| | 4974 | Died spontaneously, no TB lesions | | | | |
| | 4975 | + | (+) | 0 | 0 | 0 |
| | 4976 | + | (+) | 0 | 0 | 0 |
| PAS 50 mg.<br>100 mg.<br>150 mg. | | all animals died spontaneously with extensive TB lesions | | | | |
| Tb I plus PAS $\overline{aa}$ | | | | | | |
| 50 mg. | K 25 | + | + | 0 | 0 | 0 |
| | K 26 | + | + | 0 | 0 | + |
| | K 27 | Died spontaneously | | | | |
| | K 28 | + | + | 0 | 0 | 0 |
| 100 mg. | K 29 | Prematurely; died spontaneously, no TB lesions | | | | |
| | K 30 | + | + | 0 | 0 | 0 |
| | K 31 | + | + | 0 | 0 | 0 |
| | K 32 | + | + | 0 | 0 | ? |
| 150 mg. | K 33 | Died spontaneously, no TB lesions | | | | |
| | K 34 | + | + | 0 | 0 | ? |
| | K 35 | Died spontaneously | | | | |
| | K 36 | + | + | 0 | 0 | 0 |

experiment are presented in the table. As may be seen, both streptomycin and Tb I exerted an effect upon the experimentally produced tuberculous infection of the guinea pigs. As the activity of Tb I could be detected even in very severe infections, it was reasonable to assume that it would be detectable in tuberculosis in humans.

The results of another experiment in which Tb I, PAS, or the two drugs together were administered to one of three groups of tuberculous animals may be seen in table 2. A comparable experiment in which bovine tubercle bacilli were used may be seen in table 3.

In these experiments the combination of PAS and Tb I exerted a greater effect than PAS alone, but not greater than Tb I alone.

The further action of Tb I in severe infections in the guinea pig with the human type was further shown by the following experiments, which may serve as examples of the numerous ones carried out:

*Experiment of February 16, 1949:* Guinea pigs were infected in the flexure of the groin with 1 mg. of the human-type tubercle bacilli and, subsequent to the infection, were treated thirty times with Tb I during the period between February 7 and March 30, 1949. Autopsy was performed on July 7, 1949.

*Post-mortem findings:*

| | | |
|---|---|---|
| *Control 4079:* | Injection site: | Cheesy necrosis, numerous epithelioid nodules in the surroundings. |
| | Lung: | Numerous epithelioid nodules. |
| | Spleen: | Also numerous epithelioid nodules and necrosis. |
| | Liver: | Individual epithelioid nodules. |
| | Kidney: | No pathological findings. |
| *Animal 4083 Tb I, 2 mg.:* | Injection site | Cheesy necrosis, extensive epithelioid nodules and increase of connective tissue. |
| | Lung: | No pathological findings. |
| | Spleen: | Individual epithelioid nodules and increase of connective tissue. |
| | Liver: | Individual small remnants of loosened epithelioid nodules. |
| | Kidney: | No pathological findings. |
| *Animal 4084 Tb I, 5 mg.:* | Injection site: | Scattered discrete epithelioid nodules with increase of connective tissue in the surroundings. India-ink-storing histiocytes. |
| | Lung: | No pathological findings. |
| | Spleen: | No pathological findings. |
| | Liver: | No pathological findings. |
| | Kidney: | No pathological findings. |
| *Animal 4085 Tb I, 10 mg.:* | Injection site: | Cheesy necrosis, epithelioid nodules with increase of connective tissue in the surroundings. India-ink-storing histiocytes. |
| | Lung: | Occasional, somewhat thickened septa and individual giant cells, no typical epithelioid nodules. |
| | Kidney: | No pathological findings. |
| | Spleen: | Individual, small atypical nodules. |
| | Liver: | Individual discrete and atypical nodules. |
| *Animal 4086 Tb I, 25 mg.:* | Injection site: | Individual atypical epithelioid nodules. Strong connective tissue proliferation. |
| | Lung: | Individual atypical nodules with thickening of the septum. |
| | Kidney: | No pathological findings. |
| | Spleen: | Smallest individual nodules. |
| | Liver: | No pathological findings. |

| | | |
|---|---|---|
| *Animal 4087 Tb I, 50 mg.:* | Injection site: | Scar tissue enclosing a small area of cheesy necrosis and in the scar tissue giant cells and india-ink-storing histiocytes. |
| | Lung: | Atypical granulation tissue. No typical epithelioid nodules. |
| | Spleen: | No pathological findings. |
| | Liver: | No pathological findings. |
| | Kidney: | No pathological findings. |
| *Animal 4088 Tb I, 150 mg.:* | Injection site: | Only scar-centers with india-ink-storing histiocytes. No epithelioid nodules. |
| | Lung: | Individual small scar-centers. No tuberculous nodules. |
| | Kidney: | No pathological findings. |
| | Spleen: | No pathological findings. |
| | Liver: | Individual small infiltrations of round cells; no tuberculous centers. |
| *Animal 4090 Tb I, 200 mg.:* | Injection site: | Cheesy necrosis, scar tissue in the surroundings. No epithelioid nodules. |
| | Lung: | No pathological findings. |
| | Kidney: | No pathological findings. |
| | Liver: | No pathological findings. |
| | Spleen: | No pathological findings. |

A similar type of experiment may be seen in table 4.

The mode of action of the thiosemicarbazones in tuberculous infection has not yet been established. In my opinion, however, the therapeutic effects observed are the result of a direct action of these compounds on the tubercle bacillus itself and not a consequence of some theoretical indirect action upon the host.

In addition to inhibiting the growth of tubercle bacilli, Tb I produces: (*1*) morphological alterations, abnormal size and granular disintegration, as well as thread formation on the bacilli; further, disintegration into cocci-like structures; and (*2*) changes in the staining properties. The tubercle bacilli first lose their capacity for taking on the Ziehl stain, then also that of Gram, and finally they can be detected only in a fluorescence microscope.

The degree of the markedly strong specific action of the thiosemicarbazones upon tubercle bacilli may be seen from the experimental data presented in table 5.

The results of experiments on the addition of *p*-aminobenzoic acid to cultures containing tubercle bacilli and various concentrations of Tb I, streptomycin, or PAS are presented in table 6.

As may be seen (table 6) on an egg culture medium containing *p*-aminobenzoic acid, *p*-aminosalicylic acid shows an inhibition value which lies at 1:5,000 or even lower, streptomycin shows an inhibition of the growth of tubercle bacillus at from 1:50,000 to 1:100,000, while Tb I in solution still shows it at 1:300,000. Here we already see the same gradations which are obtained on administration in humans, in order to obtain a therapeutic effect in tuberculous infections. With PAS the largest daily dose is necessary, that is, 5 to 10 Gm. daily; with streptomycin, 1 to 2 Gm., with Tb I, only 0.1 to 0.2 Gm. Tb I therefore is more effective by weight even in a dose 100 times smaller than that of PAS.

## TABLE 4

*Guinea Pig Tuberculosis Experiment of July 13, 1948 (E 2749)*

Animals were infected in the groin with 1 mg. of the human-type tubercle bacilli. Subsequent to the infection they were treated from July 14 to September 21, 1948, 50 times with Tb I

| ANIMAL NO. | TB I TREATMENT | INJECTION SITE | | LYMPH NODE | | SPLEEN | | LIVER | | LUNG | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | gross | microscopic | gross | microscopic | gross | microscopic | gross | microscopic | gross | microscopic |
| 1275 | Control | Caseation, granulation-tissue | Caseation, epith. nodules | Pea-size black | Numerous epith. nodules<br>Giant cells | Nodules and necrosis | Numerous epith. nodules. Some necrosis. | Some nodules | Some epith. nodules | Caseous nodules | Numerous epith. nodules<br>In part small necrosis |
| 1276 | Control | Black-colored granulation-tissue | Numerous epith. nodules with giant cells, necrosis | Pea-size | Numerous epith. nodules with giant cells, necrosis | Enlarged nodules | Epith. nodules<br>Necrosis | N.p.F. | Numerous epith. nodules, necrosis | Some nodules | Epith. nodules with necrosis |
| 1279 1% | 5 mg. | +++ | Necrosis, epith. nodules | Pea-size | Numerous discrete epith. nodules | +++ somewhat enlarged | Extensive necrosis, epith. nodules | +++ | Necrosis | + | Some epith. nodules, thickened septa |
| 1280 1% | 5 mg. | Caseous center | Large caseous epith. nodules | Bean-size | Caseous centers and epith. nodules | Markedly enlargod, necrosis | Necrosis | Numerous necrotic areas | Necrosis | Caseous nodules | Epith. nodules |
| 1281 1% | 10 mg. | Small caseation, granulation-tissue colored black | Caseation epith. nodules, connective tissue | Full rice-grain size | Discrete epith. nodules, connective tissue | N.p.F. | Epith. nodules, some necrosis | N.p.F. | N.p.F. | Nodules with caseous centers | Pneumonic infiltrates, no nodules |
| 1282 1% | 10 mg. | Colored black, granulation-tissue center | Caseation, india-ink-storing histiocytes | Bean-size | Discrete epith. nodules, increase of connective tissue | Some nodules | Some resolved nodules, connective tissue developed | N.p.F. | N.p.F. | Small nodules | Thickened septa, pneumonic areas |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1283 1% | 25 mg. | Some india-ink, small area of caseation | Connective tissue increased, no epith. nodules | Bean-size | Several greatly resolved nodules | Some nodules | Residues from epith. nodules, connective tissue. | Some thickened nodules | N.p.F. | N.p.F. | No nodules, no epith. nodules, somewhat thickened septa |
| 1284 1% | 25 mg. | Granulation-tissue | No epith. nodules, compact connective tissue | Not enlarged | Some greatly resolved nodules | Some nodules | Small epith. nodules, increase of connective tissue | N.p.F. | N.p.F. | Small scar | Atypical centers |
| 1285 2% | 50 mg. | Granulation-tissue | Atypical epith. nodules, india-ink-storing histiocytes | Not enlarged | Some epith. nodules with marked development of connective tissue | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. |
| 1286 2% | 50 mg. | Scar | India-ink-storing histiocytes in one scar | Not enlarged, normal | Some india-ink-storing histiocytes. No tuberculous centers | N.p.F. | N.p.F. | N.p.F. | N.p.F. | ? | Somewhat edematous, pneumonia |
| 1287 2% | 100 mg. | Some black coloration, otherwise N.p.F | Scar with granulation-tissue | Rice-grain size | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. |
| 1288 2% | 100 mg. | N.p.F. Some black coloration | Small area of caseation, no epith. nodules | Rice-grain size | N.pF. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | Somewhat thickened septa, N.p.F. |
| 1289 2% | 200 mg. | India-ink deposit | Scar with india-ink-storing histiocytes. | Rice-grain size | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. |
| 1290 2% | 200 mg. | Black coloration, N.p.F. | Scar with india-ink-storing histiocytes | Barely rice-grain size | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. | N.p.F. |

*Explanation of abbreviations:* N.p.F. = No pathological finding; epith. = Epithelioid; Black coloration or colored black = Colored black as a result of addition of india ink to the injected culture.

Since the substances active *in vitro* against tubercle bacilli, with their entirely different chemical constitutions, also possess different points of attack, it is naturally also possible to think of combining several of them. That Eleudron and the salfathiodiazoles, as well as *p*-aminosalicylic acid, behave entirely differently than the active thiosemicarbazones and streptomycin is shown unequivocally from the fact that their action in a test-tube experiment is reduced from

TABLE 5

*Experiments on May 5, 1949 with Tubercle Bacilli of the Human Type*

| | Dilution of culture medium with NaCl | | | | | |
|---|---|---|---|---|---|---|
| | 1:5,000 | | 1:10,000 | | 1:25,000 | |
| | Second Week | Third Week | Second Week | Third Week | Second Week | Third Week |
| Culture medium (a) without *p*-aminobenzoic acid | | | | | | |
| Tb I | 0 | 0 | 0 | 0 | 0 | 0 |
| Tb IV (sulfone amide compound) | 0 | 0 | 0 | 0 | 0 | 0 |
| TB VI (a water-soluble thiosemicarbazone) | 0 | 0 | 0 | 0 | 0 | 0 |
| U 958 (*p*-aminosalicylic acid) | 0 | 0 | 0 | 0 | 0 | 0 |
| V 904 (Tb I in solution) | 0 | 0 | 0 | 0 | 0 | 0 |
| Streptomycin | 0 | 0 | 0 | 0 | 0 | 0 |
| Control animals | ++ | +++ | | | | |
| Control animal | ++ | +++ | | | | |
| Control animal | ++ | +++ | | | | |
| Control medium (b) with *p*-aminobenzoic acid 1:10,000 | | | | | | |
| Tb I | 0 | 0 | 0 | 0 | 0 | 0 |
| Tb IV | 0 | + | ++ | ++ | ++ | +++ |
| Tb VI | 0 | 0 | 0 | 0 | 0 | (+) |
| U 958 | 0 | 0 | + | ++ | ++ | +++ |
| V 904 | 0 | 0 | 0 | 0 | 0 | 0 |
| Streptomycin | 0 | 0 | 0 | 0 | 0 | 0 |
| Control animal | ++ | +++ | | | | |
| Control animal | ++ | +++ | | | | |
| Control animal | ++ | +++ | | | | |

*Explanation of symbols:* +++ = Very large growth of bacilli; ++ = Large growth of bacilli; + = Slight growth of bacilli; 0 = No growth of bacilli.

about from 1:25,000 to 1:100,000 down to 1:5,000 by the addition of *p*-aminobenzoic acid. This is not the case with streptomycin and thiosemicarbazones. On the contrary, in a number of guinea pig experiments, in which the animals were given food containing *p*-aminobenzoic acid, particularly good results were obtained with the thiosemicarbazones as well as with streptomycin and the combination of Tb I and streptomycin.

A combination of *p*-aminosalicylic acid and streptomycin is also possible, or one of Tb I with streptomycin. In our experimental procedure we did not, it

TABLE 6

*Inhibition of the Growth of Tubercle Bacilli of the Human Type on Egg Culture Media with and without the Addition of P-aminobenzoic Acid in the Presence of Tb I, Streptomycin, or P-aminosalicylic Acid, respectively, in the Concentrations Indicated*

| | WITHOUT ADDITION OF *p*-AMINOBENZOIC ACID | | WITH ADDITION OF *p*-AMINOBENZOIC ACID | |
|---|---|---|---|---|
| | First reading January 27, 1949 | Second reading February 3, 1949 | First reading January 27, 1949 | Second reading February 3, 1949 |
| *Tb I* in Formamide | | | | |
| 1: 5,000 | 0 | 0 | 0 | 0 |
| 1: 10,000 | 0 | 0 | 0 | 0 |
| 1: 25,000 | 0 | 0 | 0 | 0 |
| 1: 50,000 | 0 | 0 | 0 | 0 |
| 1:100,000 | 0 | 0 | 0 | 0 |
| 1:200,000 | 0 | 0 | 0 | 0 |
| 1:300,000 | 0 | + | 0 | 0 |
| *V 751* = Tb I solution in equal parts of formamide and glycol monomethyl ether | | | | |
| 1: 5,000 | 0 | 0 | 0 | 0 |
| 1: 10,000 | 0 | 0 | 0 | 0 |
| 1: 25,000 | 0 | 0 | 0 | 0 |
| 1: 50,000 | 0 | 0 | 0 | 0 |
| 1:100,000 | 0 | 0 | 0 | 0 |
| 1:200,000 | 0 | 0 | 0 | 0 |
| 1:300,000 | ? | + | 0 | 0 |
| *Streptomycin* | | | | |
| 1: 5,000 | 0 | 0 | 0 | 0 |
| 1: 10,000 | 0 | 0 | 0 | 0 |
| 1: 25,000 | 0 | 0 | 0 | 0 |
| 1: 50,000 | 0 | + | 0 | 0 |
| 1:100,000 | 0 | ++ | 0 | 0 |
| 1:200,000 | (+) | +++ | + | +++ |
| 1:300,000 | + | +++ | ++ | +++ |
| *Tb I powder* | | | | |
| 1: 5,000 | 0 | 0 | 0 | 0 |
| 1: 10,000 | 0 | 0 | 0 | 0 |
| 1: 25,000 | 0 | 0 | 0 | 0 |
| 1: 50,000 | 0 | 0 | 0 | 0 |
| 1:100,000 | 0 | 0 | 0 | 0 |
| 1:200,000 | 0 | 0 | 0 | 0 |
| 1:300,000 | ? | + | 0 | 0 |
| *p-aminosalicylic acid* | | | | |
| 1: 5,000 | 0 | 0 | (+) | +++ |
| 1: 10,000 | 0 | 0 | + | +++ |
| 1: 25,000 | 0 | 0 | ++ | +++ |
| 1: 50,000 | 0 | 0 | ++ | +++ |
| 1:100,000 | 0 | 0 | ++ | +++ |
| 1:200,000 | 0 | 0 | ++ | +++ |
| 1:300,000 | 0 | 0 | +++ | +++ |
| *Tb IV* | | | | |
| 1: 5,000 | 0 | 0 | ++ | +++ |
| 1: 10,000 | 0 | 0 | ++ | +++ |
| 1: 25,000 | 0 | 0 | ++ | +++ |
| 1: 50,000 | 0 | 0 | ++ | +++ |
| 1:100,000 | (+) | ++ | ++ | +++ |
| 1:200,000 | + | +++ | ++ | +++ |
| 1:300,000 | ++ | +++ | +++ | +++ |

is true, see anything of such a powerful increase of the action as Heilmeyer mentions from a combination of Tb I and PAS. From our experimental result it appears most advantageous, if necessary, to use the combination of thiosemicarbazone with streptomycin. This is based on the deduction that streptomycin, so beneficial and valuable as such, does not act uniformly in all organs. Baggenstoss, Feldman, and Hinshaw have already pointed out that it is difficult to explain why the tuberculous centers in some organs are made fibrous by streptomycin treatment and heal in this manner, but do not in other organs. Our experimental investigations gave us some informative hints for explaining this fact. We saw that under streptomycin treatment lung centers healed much sooner than spleen centers; that in the spleen a marked coarsely nodular tuberculosis was sometimes even developed.

If a one per cent solution of streptomycin is allowed to act upon tubercle bacilli, then, with action for four weeks or even eight weeks, no destruction of the infective power of the tubercle bacilli can be determined. Tubercle bacilli, on which one per cent Tb I dissolved in ethylene glycol had acted, were no longer infectious after a short period of action. With a period of action of more than twenty-four hours, a one per cent solution of PAS does not show any action; this occurs only after a duration of exposure of from four to eight weeks.

Streptomycin possesses an entirely different mechanism of action than Tb I and PAS. In animal experiments streptomycin is materially more effective than PAS. It has not been completely clarified why in animal experiments PAS, in comparison with Tb I and streptomycin, has such a slight action against infections with the human type and even less action against infections with the bovine type. It is conceivable that sufficient quantities of *p*-aminobenzoic acid, or of similar antagonists of PAS, occur in the body to annul the action of the PAS, as was shown in the culture experiments. Tests should now be made to learn whether calcium salts, which reduce the action of *p*-aminobenzoic acid upon PAS, make it possible to attain more successful cures in animal experiments. By the addition of calcium succinate and other substances, we were able *in vitro* to eliminate, at least in part, the deleterious effects of the *p*-aminobenzoic acid on the activity of PAS.

The failures of Tb I could usually be explained on the basis of special anatomical reasons. The action of Tb I is insufficient, if the infection is such that extensive cascations occur at the injection site so that the medicament does not reach it in sufficient concentration. The same is the case in sufficiently large areas of caseation which occur by aspiration from cavities rich in bacilli. This danger exists not only with cavities, but also in caseation centers rich in bacilli which are in connection with a bronchus, and particularly also in caseous bronchitis. In staining the material from such centers, I was always astonished by the enormous quantities of bacilli which could be found. Even streptomycin and Tb I cannot protect against such massive dispersions of bacilli. For it is possible that even bacilli whose virulence has been greatly weakened—or even killed bacilli—may during the disintegration of their body-substance still give rise to tissue destruction in the presence of hypersensitization.

If epithelioid nodules are already present in the various organs at the begin-

ning of the Tb I treatment, then they show peculiar regressive phenomena. Under the effect of the Tb I, the epithelioid nodules undergo a weblike resolution in which the epithelioid cells shrink and finally are completely destroyed. The centers become surrounded by, and infiltrated with, connective tissue. The giant cells resist for the longest time; they gradually also lose their typical appearance of the Langhans' giant cell and rather take on the character of foreign-body giant cells, then degenerate and likewise disappear. With the presence of large caseated centers at the beginning of the treatment, connective-tissue encapsulating of the center occurs. As long as these caseous foci exist, there is a potential danger of the formation of new lesions either by direct extension or by the hematogenous route.

In regard to the clinical uses of such drugs as Tb I, I should first like to be entirely sure that the new methods of treatment do not produce undesired secondary effects of late consequences which are not always detected in animal experiments. If in such a therapy we breed resistant strains of tubercle bacilli, as has already occurred with streptomycin, the present blessing could grow into a curse. Consequently, the thiosemicarbazones have been used principally in such patients as could no longer be helped by any other known method. Now, after two to three years of clinical experience, it is to be hoped that the basis of the treatment can gradually be broadened, but even now it will remain desirable to hold the treated patients under clinical guardianship, at least until they can be declared to be free from bacilli and cured clinically.

A later main aim of the chemotherapy of tuberculosis must be to prevent altogether the development of infectious, so-called "open" tuberculosis cases, regardless of whether this goal is reached with one chemotherapeutic agent alone or with a combination of several of them. Early treatment presupposes early recognition. Every method, regardless of whether of a surgical or chemotherapeutic nature, should endeavor to attain as its aim: (*1*) to make open tuberculosis cases unequivocally free from bacilli and to discharge them only thereafter; (*2*) with early recognition to prevent entirely the development of the so-called "open" tuberculosis cases.

The value of a method of treatment of tuberculosis, regardless of type, should be judged solely from this point of view, for only after we fulfill these minimum requirements can we entertain the hope of gradually conquering tuberculosis.

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# THE PRESENT STATUS OF THE CHEMOTHERAPY OF TUBERCULOSIS WITH CONTEBEN, A SUBSTANCE OF THE THIOSEMICARBAZONE SERIES[1,2]

**A Review**

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## INTRODUCTION

Among the few substances active chemotherapeutically which exert an effect upon the tubercle bacillus not only in *vitro*, but also *in vivo*, 4-acetylaminobenzaldehyde thiosemicarbazone (Conteben) has recently gained considerable interest. Thus far more than 10,000 patients with different forms and stages of tuberculosis have been treated with this chemotherapeutic agent which has been tested clinically under the laboratory designation "TbI/698." Over sixty clinical papers in part already published and in part still in press report on the present status of the experiences with thiosemicarbazone therapy in Germany. It therefore seems possible to render a broad-gauged, careful judgment of the clinical performance and limits of this preparation.

In this large-scale investigation, the present writers have been responsible for the allocation of the drug and for the collection and analysis of the individual clinical reports submitted by the various investigators. The present communication represents a summary review of this material. No attempt has been made to review the published reports individually, but a complete list of all publications in the German literature on the subject is included under the bibliography.

*General considerations:* It lies in the nature of tuberculosis as a severe general, usually chronic, disease, that the word "cure" by means of a chemotherapeutic agent must be applied with great reservation after only two to three years of clinical experience. In the evaluation of the clinical effectiveness of thiosemicarbazone therapy it is of importance that the majority of the patients whose condition could by means of this preparation be improved, at present with clinical freedom from symptoms, had previously, without chemotherapy, been unsuccessfully treated for a long time (in part, more than a year) in sanitoriums or hospitals.

Of all forms of tuberculosis, the fact appears most clearly in the foreground in pulmonary tuberculosis that the response of the infection to thiosemicarbazone therapy is essentially a question of the respective reaction power of the tissue. The more labile the process of the disease and the better the blood supply, the more promising thiosemicarbazone therapy seems to be. Extensive caseous processes, however, respond less favorably to the medication. According to present

[1] From the Laboratories of the Farbenfabriken Bayer at the Elberfeld Works, Leverkusen, Germany.

[2] The translation of this article into English was obtained through the courtesy of Schenley Laboratories, Inc., New York, N. Y.

experiences, the least prospects for an effect by Conteben are presented by instances of chronic pulmonary tuberculosis.

Nothing definite can as yet be said about the mode of action of thiosemicarbazone therapy. The extraordinarily small dosage which comes under consideration in the treatment of adults (12.5 to 200, or even 300 mg. per day) is remarkable in comparison with the tuberculostatic effectiveness of the preparation determinable *in vitro*. The daily average dose of thiosemicarbazone, therefore, amounts to about one-tenth (by weight) that required for streptomycin. A further material difference between Conteben and streptomycin consists in the fact that drug-resistant tubercle bacilli have thus far not been detected in treatment with Conteben.

## SUMMARY OF THERAPEUTIC STUDIES

*Miliary and meningeal tuberculosis:* The unequivocally slower onset of the thiosemicarbazone effect, detectable subjectively and objectively, as compared with streptomycin is worthy of note. Hence, acute generalized miliary tuberculosis and tuberculous meningitis are two forms of the disease which are not to be included among those where Conteban is indicated. Other tuberculous manifestations, such as tuberculous tissue changes of the mucous membranes (larynx, tracheobronchial, intestinal, and bladder tuberculoses), however, usually respond impressively to Conteben.

Everything seems to point to the fact that the thiosemicarbazones, as well as streptomycin and para-aminosalicylic acid, possess different modes of action upon the tubercle bacillus and the tuberculous infection. Consequently, the possibilities of an intelligent combination of these chemotherapeutic agents become obvious. It will be the task of additional clinical observations to determine in which forms and stages of tuberculosis the individual chemotherapeutic agents, recognized as possessing activity, deserve preference and when a combination thereof promises an enlargement of the range of action in the chemotherapy of tuberculosis.

*Pulmonary tuberculosis:* Recently developed exudative type pulmonary processes frequently show unusually rapid recession under thiosemicarbazone therapy. The result shows itself in a prompt improvement of the general conditon, increase in appetite, and frequently an astonishing increase in weight. Objectively, in addition to the recession of the infiltration, as shown roentgenologically, a rapid effect upon the temperature is evident.

The sure evaluation of the action of thiosemicarbazone in the cavernous processes presents great difficulties. In view of the known tendency of cavities to undergo spontaneous recession, only such cases can be drawn on for evaluation whose unequivocally progressive character has been made certain by a preliminary observation period of sufficient length. At present there are available experiences with a large number of cavernous pulmonary processes with an unequivocal tendency toward improvement (in part under pretreatment observation for 12 months) during the course of the use of thiosemicarbazone for several months. A complete recession of the cavities presumably to the formation

of scar tissue has been demonstrated tomographically in some instances. It is of importance that the treatment must not yet be interrupted at this point. Instead, the patient must be treated further for several months beyond the stage of clinical freedom from symptoms in order to keep the result attained. A tuberculous process, even after apparently complete recession of a large cavity and with the sputum becoming negative for tubercle bacilli, can again become active with renewed cavity formation by premature cessation of the Conteben medication. Consequently, the drug must be continued for at least six months, although in small doses (25 to 50 mg. per day), even after clinical and roentgenological arrest of the lesion.

*Disappearance of bacilli from sputum:* For evaluating the action of thiosemicarbazone therapy, the sputum findings (smears and cultures) during the treatment form a particularly important criterion. In a whole series of cases without collapse therapy and solely under the action of the antimicrobial agent, the sputum became negative for acid-fast bacilli on smear even within the first month of the treatment, but in general only within the first three months of the treatment. It is of importance that the sputum frequently becomes "negative", although cavities can still be detected. In processes with cirrhotic changes, in which encapsulation of the cavities in connective tissue is probable, the sputum becomes negative only relatively late. This also occurred in all cases in which the Conteben treatment was transiently interrupted prematurely.

*Morphologic changes in bacilli:* Not only the reduction in the number of bacilli in the sputum, but also their changes in shape are considered to be an important indication of the effectiveness of Conteben. The tubercle bacilli lose their characteristic shape and especially their capacity for taking stains. The rodlets, generally with sharp contours and homogeneously stained, become weakly-stained structures, partly bent, partly threadlike, partly "blown up," and not rarely containing polar bodies, or are completely resolved into granules. It is of paramount importance that a "sputum negative" by Ziehl-Neelsen stain can still be recognized under a fluorescent microscope for a long time as being "positive," and that similar changes in form, even though to a materially smaller degree, may also appear without the use of chemotherapy.

*Chronic hematogenous disseminated pulmonary tuberculosis:* Seen in an over-all picture, chronic hematogenous disseminated pulmonary tuberculosis likewise responds quite well to Conteben. In general, however, it is possible only in a small number of cases to make the sputum negative. The fact that these exudative forms of pulmonary tuberculosis, in part highly active, can be converted into more productive forms is of special clinical importance, and also the fact that in severe cavernous phthisis the progress of the tuberculous process can be held back. Hence by the use of the drug these cases may be brought to the stage where operations can be carried out. Here it is considered essential that it is frequently possible in these cases, before the operation, to bring about such a far-reaching recession of the tuberculous process by the action of thiosemicarbazone that the necessary surgical procedure may be less extensive. That chemotherapeutic pretreatment of the patients by stabilization of the defense condition of the

host contributes in many cases to a diminution of the surgical risk is considered to be a further noteworthy advantage. Nevertheless, in some of the patients it is not possible in this manner to produce elimination of the cavities. Here local chemotherapy, by the intracavernous application of the drug, presents a further possibility of obtaining action upon this severe form of tuberculous tissue change.

*Intracavitary instillation:* According to the experiences thus far, impressive results are obtained if supplementing cavity drainage according to Monaldi, from 0.1 to not more than 0.2 Gm. of finely powdered Conteben, suspended in from 1 to 2 cc. of pure glycerol, are instilled into the cavities. In an entire series of cases, complete bacteriologic disinfection of the cavities has been obtained by this method, accompanied by shrinkage of the same, whereby particularly severe cases again became ready for operation. In one series of cases, by use of combined peroral and intracavernous thiosemicarbazone therapy thus carried out, diminution of the cavity was obtained before the collateral bronchus was closed. For understandable reasons, the use of pure glycerol readily leads to an increased tendency to cough. In such cases it has therefore proved advantageous to make the suspensions with physiological salt solution instead of with pure glycerol. The results of this intracavernous therapy could be confirmed in a small series of cases by pathologic-anatomical examinations. Tubercle bacilli could no longer be detected. The circumcavernous, tuberculous centers were surrounded by connective tissue or completely resolved and converted into scar tissue. Instead of using the drug in a liquid suspension, it is also possible to blow Conteben powder into the cavity, provided a Maurer cavernostomy is undertaken and sufficiently broad drainage is obtained.

Seen as a whole, caseous pneumonia is not a gratifying field of indication for the use of Conteben. With the assumption that the diagnosis can be made before the extensive exudates have become massively caseous, *fresh* exudative pneumonia may be influenced quite impressively by Conteben. The coarsely nodular, predominantly caseous exudative forms of pulmonary tuberculosis, like caseous bronchopneumonia (the prognosis of which is frequently made worse by specific intestinal and laryngeal complications) could, as expected, not be affected to a noteworthy degree by Conteben. In these cases the process has continued to progress even under the therapy, the quantity of expectoration has remained unchanged, and the fever and the erythrocyte sedimentation rate have been unaffected. It is, however, noteworthy in these cases that the laryngeal and intestinal processes are sometimes improved to the point of complete absence of clinical symptoms, in spite of the continuing progression of the pulmonary lesions.

As expected, cirrhotic pulmonary processes with shrinkage of the neighboring organs do not respond markedly to Conteben. According to the experience gained thus far, the only effects noted in such cases have been upon fresh exudative areas accompanying the old fibrotic disease.

*Empyema:* In tuberculous empyema or pyopneumothorax, *local* Conteben therapy in the form of intrapleural instillation of a suspension of 0.1 to not more than 0.5 Gm. of the finely powdered drug in physiological salt solution has been followed with favorable results. This local therapy is, in general, carried out three

times per week and is continued until new formation of exudate decreases. Usually instillations only once or twice a week suffice until the purulent exudate becomes serous or disappears entirely. In order to obtain as uniform an admixture as possible with the exudate, or complete bathing of the pleura with the drug suspension, it has been found to be advantageous to subject the patient to a so-called "rolling treatment." A prerequisite for clinical success is, however, that no mixed infection must be present or must be previously removed. For such purpose the intrapleural use of penicillin, if necessary, supported by parenteral injections of this antibiotic, have proved to be quite effective. As a further prerequisite for such success, closure of the perforations is required in any empyemas which were produced by rupture of cavities. On the whole, the results of intrapleural treatment with Conteben are first seen in the fact that tubercle bacilli can no longer be detected in smears. Later *cultures* for tubercle bacilli also remain negative, although the exudate is usually still purulent; and finally, new formation of exudate slows down and then disappears completely.

*Tracheobronchial tuberculosis:* The particularly good action upon all tuberculous mucous membrane processes by thiosemicarbazone is also shown by the results obtained in the treatment of tuberculous tracheobronchitis and bronchial tuberculosis. The best tendency toward healing has thus far been observed in clinically solitary tuberculosis of the large bronchi or of the trachea, with consistently "positive" sputum from more or less superficial or deep mucous membrane abscesses. Tuberculosis of the large bronchi, which accompanies extensive, open cavernous pulmonary tuberculosis, as would be anticipated, was only slightly affected by the drug although, here too, occasional partial successes were obtained.

*Laryngeal tuberculosis:* The special role which all tuberculous mucous membrane processes play within the range of Conteben therapy has been shown particularly in laryngeal tuberculosis.

In addition to the regularity with which laryngeal tuberculosis responds to the treatment, the rapidity with which the initiation of the action shows itself is particularly remarkable. The pain on swallowing frequently disappears after one to two days, at the latest, during the first week of the treatment. The disappearance of the dysphagia caused by the losses of epithelium is designated to be as unequivocal as previously was observed only by an interruption of the nervous laryngicus cranialis. Correspondingly, the treatment of the dysphagia heretofore generally necessary before meals with all patients with severe laryngeal tuberculosis has usually proved to be entirely superfluous after treatment with thiosemicarbazone for only one week. With the disappearance of the dysphagia, the unpleasant secretion of mucus also decreased. The next findings to be observed are recession of the infiltrative edema at the epiglottis and arytenoid region. Regeneration of the epithelium follows astonishingly rapidly, whereby the picture of a macroscopic freedom from symptoms is also attained. Only in those cases in which the epiglottis has already been extensively destroyed could healing with the formation of scars be observed. The freedom from symptoms is, however, not unconditionally identical with a complete clinical cure. Rather, treatment for

months beyond the stage of clinical freedom from symptoms is necessary in order to prevent relapses as a result of reactivation of residual nodules in the depth of the tissues. Particularly in view of the danger of relapses, laryngeal tuberculosis must not be treated solely by local dusting on of finely powdered Conteben, because local treatment of laryngeal tuberculosis does not appear always to possess the necessary deep action. The advantage of local application is frequently the particularly rapid and impressive effect upon the subjective complaints. The treatment should therefore best be carried out locally and orally in combination. Here, it must, however, be considered that a part, i.e., about one-half of the preparation applied locally, is swallowed by the patient and hence gets to exert its action through the blood circulation. This must be taken into consideration in determining the oral dose.

*Intestinal tuberculosis:* A further serious complication of pulmonary tuberculosis which proved to be responsive to therapy is intestinal tuberculosis. Heretofore, active intestinal tuberculosis was deemed to be a contraindication to surgical intervention in the lungs. Under the protection of the action of thiosemicarbazone, however, a material enlargement of the range of indications for operation have resulted. The duration of the treatment which is necessary for an effective action upon even the most severe intestinal tuberculosis, clinically and roentgenologically diagnosed in patients with open pulmonary tuberculosis, fluctuates according to Boehm and Kuhlmann between ten and eighteen weeks. Within this time the pains and spasms disappear first, insofar as they are present. This generally occurs during the first ten days. At the same time, defervescence, or reduction of temperature, is attained. The diarrhea usually ceases within fourteen days, and at this point the pathological roentgenographic findings in the intestines generally begin to disappear. Between the eighth and fourteenth weeks the roentgenographic findings in the intestines usually become so much improved that it is now possible to speak of "residual findings" or of scarlike residues.

A survey of the magnitude of the drug effect upon the intestinal tuberculosis is supplied by examination of pieces of intestine which had to be excised because of the occurrence of stenoses during the course of the healing process under Conteben therapy. In the small intestine, Letterer was able to find only small radiating scar residues. In the large intestine small, polypous proliferations of the mucous membrane were found which were assumed to represent sites of previous abscess formation. The base of the "abscess," however, was completely filled with replacement tissue and covered with a mucus-like membrane.

In one of the preparations the serous side of the small intestines presented a picture which was in remarkable contrast to the striking results of healing on the mucous membrane side. The lymph passages could be seen as small caseous foci. Small yellowish-white tubercles were still distinctly recognizable, so that the macroscopic impression did not at first lead to the conclusion that healing had occurred. The microscopic picture, however, showed in an astonishing manner a marked tendency toward scar formation around all the tubercles. A continuous circular connective-tissue constriction of the caseated tubercle and a proliferation

of reticular and collagen fibers were present, so that the entire center was enclosed. The fresher tubercles, still predominantly in a cellular condition, likewise revealed evidence of ciratization phenomena, for recticular and collagen fibers were present, not only outside, but also inside the tubercles. In addition, the development of new capillaries in the area of the region of the tubercles could be detected. According to Letterer, Conteben reinforces the healing tendencies of the tissue in a *perfectly natural* manner. He therefore is in complete agreement with the investigations of Domagk in guinea pigs.

Intestinal tuberculosis also often requires treatment for months beyond the stage of clinical freedom from symptoms, in order to prevent relapses.

*Genitourinary tuberculosis:* According to Boshamer, the mucous membrane of the bladder, the ureters, and the urethra exhibits a particularly good tendency toward healing under thiosemicarbazone therapy. Thus, even with still existing bacilluria from the kidney, tuberculous bladder ulcerations have been healed during the peroral administration of Conteben. In case the severest forms are not present, the tuberculous nodules usually heal within one to two months. Usually the bacilluria disappears only after three to four months. This effect of thiosemicarbazone is deemed to be essential in so far as participation of the bladder in the tuberculous infection has not permitted as prompt an operation as possible. Boshamer believes that under the protective action of the drug upon the mucosal lesions of the bladder, he can now select the most favorable time for the operation. Further experience in this doubtlessly important field of indications must, however, show to what extent this assumption is justified. In bladder tuberculosis with mixed infection, the secondary infection must first be eliminated, as in pleural empyema, before the effect of local thiosemicarbazone therapy (instillation) can be expected. For this purpose, in addition to the intravesical use of polyvalent sulfonamides (such as Marbadal), penicillin has proved to be satisfactory.

Tuberculosis of the kidneys belongs among the forms of tuberculosis most difficult to control chemotherapeutically. The experiences thus far with Conteben are encouraging and justify a further thorough application in this condition. Thus, histologic examinations of excised kidneys after the utilization of thiosemicarbazone suggest that the tuberculous foci in the kidney are replaced by connective tissue under the action of the drug. Even certain abscess cavities are believed to have been converted to connective tissue. The cavities are, however, not caused to disappear, but remain existing as hollow spaces encapsulated in connective tissue. In general, the bacilluria disappears within four months, even when large kidney abscesses are present. If, however, an active focus is present elsewhere, as, for example, a pulmonary cavity, then the tubercle-bacilluria cannot be affected by oral thiosemicarbazone administration.

*Miscellaneous forms of tuberculosis:* Nothing final can as yet be said about the responsiveness of tuberculosis of the serous membranes to thiosemicarbazone therapy. At all events, it is worth mentioning that tuberculous peritonitis in a few instances, and especially fistulating peritoneal tuberculosis, has responded very well.

The action of thiosemicarbazone upon bone and joint tuberculosis cannot yet be clearly seen. The particular anatomical conditions in this manifestation of tuberculosis, i.e., the possibility that the antimicrobial agent reaches the tuberculous foci via the circulation of the blood in only low concentrations, limits the prospects of success of chemotherapy from the start.

Tuberculosis of the skin, particularly lupus vulgaris, belongs among the forms of tuberculosis in which very extensive and favorable clinical experiences are available. They represent a completely assured indication for the preparation. It would, however, go beyond the scope of this summarizing presentation to go into details thereon.

The experiences thus far in juvenile tuberculosis do not yet suffice for a judgment, even though a series of quite impressive results has been obtained in pulmonary and bone tuberculosis. We will therefore refrain from presenting in detail the experiences gained thus far.

*Dosage regimens:* The determination of the most appropriate dosage presented the greatest difficulties in the development of thiosemicarbazone therapy. The rule applicable from sulfonamide and penicillin therapy, that by means of sufficiently high doses bacteriostatically highly effective blood levels be obtained as rapidly as possible, does not apply in thiosemicarbazone therapy. The dosage must be made appropriate in every case to fit the individual situation in regard to the tuberculous tissue alteration and the response of the patient to the antimicrobial agent. It is recommended, therefore, that Conteben therapy be begun with the smallest initial doses, for example, from 12.5 to 25 mg. Corresponding to the effect of this medication upon the subjective and objective condition of the patient, the daily doses are then increased gradually until the therapy (without producing signs of intolerance) brings about a subjective improvement, as well as an objective improvement (decrease of the fever, improvement of the blood picture, increase in weight, improvement of the roentgenographic findings, et cetera). In general, 200 mg. per day (and in exceptional cases, 300 mg.) are deemed to be the upper limit for the daily dosage of Conteben. The average daily dose in current use is approximately 2 mg. per Kg. of body weight.

### *Toxicity of Conteben*

In judging the toxicity of Conteben, it must be considered that the most frequent and most marked untoward phenomena were observed at the beginning of the clinical testing of the preparation. During this time the preparation was still administered in combination with sulfathiazole under the temporary designation "TbI/698E." This preparation was soon discarded, however, because it did not have any advantages, and from the standpoint of toxicity possesses disadvantages. Furthermore, during the first period the preparation was used in amounts which, according to the state of our experience today, must in part be designated as a very large overdosage. This in part is due to the fact that the clinical use of thiosemicarbazone was first made in tuberculosis of the skin, especially in lupus vulgaris. As is known, tuberculosis of the skin occupies a special position among the different forms of tuberculosis and, indeed, not only in

respect to its pathogenesis, but also in respect to its response to chemotherapeutic agents. This applies also to the magnitude of the necessary therapeutic doses of Conteben and the toleration of these doses. While, for example, in lupus vulgaris daily doses of 500 mg. of Conteben were customary, in pulmonary tuberculosis this dose represents about two-and-one-half times the daily maximum dose generally recommended today.

*Gastric initiation:* The most frequent secondary effects under thiosemicarbazone medication at the beginning of treatment are lack of appetite, gastric complaints, and nausea which, particularly in certain cases, may increase to vomiting. Peculiarly, these symptoms disappear in most cases in spite of continuance of the medication. The patient becomes accustomed to the drug. Because of this, it has proved to be advantageous to start the therapy with the smallest doses and to increase gradually to the dose which, even during prolonged administration, is unequivocally comfortable but, therapeutically, is surely effective. With sensitive patients these gastric disturbances can generally be eliminated by small doses of phenylethylbarbituric acid or, better still, antihistamine drugs or digestive-enzyme preparations.

*Encephalopathy:* These complaints must, however, be evaluated more seriously if they occur during the course of a longer treatment, and especially if headaches and signs of increased intracranial pressure become associated with them. In these cases immediate interruption of the treatment is necessary. These symptoms could always be rapidly and surely controlled by intravenous infusions of sugar. But it is pointed out that this particular type of toxic reaction was only observed at the beginning of the clinical trials when considerable overdosing occurred in a few instances. It is believed that the central nervous system type of reaction can be completely avoided within the range of the dosage tested and found satisfactory during the subsequent clinical investigations.

*Conjunctivitis and exanthemata:* The appearance of conjunctivitis may be observed by the use of Conteben in large doses (300 to 400 mg. per day). On reducing the dosage, the conjunctivitis usually disappears in a short time.

Exanthemata, which are frequently preceded by conjunctivitis, occur as slightly itchy, maculopapular skin eruptions. Under the use of antihistamine drugs, the eruption usually disappears rapidly. According to the prevailing experiences, the exanthemata are to be considered not only of allergic genesis, but as medicament-exanthemata, especially if they appear after very large daily and total doses.

*Hematopoietic system:* The red and white blood cell picture has been given special attention during the clinical trials with thiosemicarbazone. In one series of cases there was a uniform drop in hemoglobin and erythrocytes. In these cases the indirect bilirubin in the serum was simultaneously increased, while urobilin and increased urobilinogen excretion in the urine occurred. During this hemolytic crisis the bone marrow showed an increased erythropoesis. All changes become equalized in spite of continued administration of thiosemicarbazone, usually, it is true, in reduced amounts. The dose of the drug and also the individual sensitivities of the erythrocytes play a role. Infectious toxic anemias, such as occur not rarely in pulmonary tuberculosis, again disappear under Conteben therapy. Seen

as a whole, anemias occur relatively rarely within the frame of the recommended and satisfactory dosage. Moderate spiculated forms, anisocytosis and poikilocytosis of the erythrocytes, generally have no serious implications and do not require discontinuance of the medication. With larger dosage (300 mg. per day and more) anemias are, however, more frequent and are determined, not only allergically, but by the overdosage.

*Agranulocytosis:* Toxic effects of thiosemicarbazone upon the leukocyte picture, considered as a whole, are relatively few. In this connection, several cases of agranulocytosis which were observed at the beginning of the treatment (after a total dose of only 0.6 to 4.5 Gm. of the drug, and with daily doses up to a maximum of 200 mg.) arouse special interest as an expression of a particular hypersensitivity of the respective patients.

Severe eosinophilia, present during the agranulocytic reaction, both in the peripheral blood as well as in the cerebrospinal fluid, has been noteworthy.

In individual patients, a gradual decrease of the leukocytes below 5,000 per cu. mm. with relative preponderance of the lymphocytes, was observed only in the course of thiosemicarbazone treatment extending over several months. No rise in the temperature occurred. In this form of agranulocytosis, there is no eosinophilia, such as seems to be the rule in the allergic form. The blood findings improved soon after discontinuing the preparation.

Up to the present, agranulocytosis was observed predominantly in female patients, which is interpreted as confirmation of the conception, generally held today, that Schultz's agranulocytosis is more common in this sex. It is recommended with all patients who are receiving treatment with Conteben that special care be taken in the use of other medicaments which are known to possess a relationship to the production of agranulocytosis.

For an early recognition of agranulocytosis which may develop in sensitized patients, determination of the total and differential leukocyte counts should be performed twice a week. Angina, pharyngitis, or gingivitis require special attention in this connection.

It is interesting to note the occasional occurrence of hypersensitivity toward albumin, especially toward old cheese and preserved fish (herring) under thiosemicarbazone medication, to which attention should be paid, especially with women. Furthermore, patients whose previous histories yield indications of urticaria, eczema, acute polyarthritis, et cetera, should be watched with especial care during the thiosemicarbazone medication.

*Question of hepatotoxicity:* The question whether and to what extent Conteben can produce damage to the liver has not yet found any uniform answer. A series of communications on liver damage in the course of the thiosemicarbazone treatment are based merely upon the pathological results of the liver function test. It must be considered, however, as already pointed out by Hurst, Maier, and Lough, that in pulmonary tuberculosis the examinations of the liver function are more frequently abnormal the more severe the cases under examination, or the more sensitive the methods for testing the liver function. Thus, for example, according to Steidl and Heise, the positive yields in the cinchophen test could be

raised to about 90 per cent, even in relatively mild illnesses. According to Hurst, Maier, and Lough, the bromosulfalein test was positive in about 41 per cent of a series of patients with tuberculosis. This shows the difficulty in judging when an abnormal finding in the liver function test in tuberculosis cases during the course of thiosemicarbazone medication can be ascribed to the preparation and when it is the expression of a liver damaged by the disease itself. Furthermore, the albumin-flocculation reactions can be used only limitedly for diagnosing liver damage. As is known, in pulmonary tuberculosis a drop in the cholesterol content of the serum represents an unfavorable prognostic sign. The finding repeatedly cited that the total cholesterol in the serum and also the ester fraction both increase under Conteben medication is therefore interpreted in part as a sign of an improvement of the tuberculosis by the drug, but in part also as a result of damage to the liver by the preparation. Finally, it is of interest that in 4 cases observed independently it was possible to act favorably upon amyloidosis by means of Conteben. This may be used as an argument against a liver-damaging effect of the preparation.

With these conditions, special significance must be ascribed to laparascopic examinations of the liver of the patients who are under thiosemicarbazone medication. The most frequent damage to the liver in tuberculosis which can be detected histologically, as is known, is the fatty liver, which is found in about one-half of the cases at autopsy. In what stage of pulmonary tuberculosis the fatty liver occurs is as little known with certainty today as the cause of its production. In autopsies on pulmonary tuberculosis cases which had been treated with Conteben for a long time it was striking that a more intensive fatty liver was present in them than is customarily seen at autopsy. Boehm, in laparotomies of patients who had been under Conteben treatment, observed that in all patients who had been treated with the drug for more than ten weeks there was present a diffuse fatty liver which appeared to bear no direct relation to the severity of the tuberculous process. Laparoscopic examinations according to Kalk made in a few of the less severe cases, which likewise had been treated with thiosemicarbazone for more than ten weeks, also revealed the presence of a diffuse yellow fatty liver. It is of importance that in none of these patients could an unequivocally pathological result of the liver function tests be obtained, nor could an enlarged liver be detected. Subsequent laparoscopic examinations in a few could an enlarged liver be detected. Subsequent laparoscopic tests in a few instances showed, however, that the fatty degenerations of the liver are reversible and can no longer be detected (laparoscopically) in the period between the tenth and twelfth weeks after discontinuing the medicament.

In this connection it is of significance that in animal experiments it is not possible with certainty to produce fatty infiltrations of the liver by means of thiosemicarbazone. It is necessary to pay special attention to the liver function during the Conteben medication, for which purpose, according to prevailing experiences, the galactose-loading test according to Pollak or Strehler is most suitable. For eliminating the disturbances of the liver function under thiosemicarbazone medication (it being immaterial whether these are a result of the medication

or of the tuberculosis) the intravenous administration of methionine in doses of from 0.8 to 2.0 Gm. per day, or the oral or intravenous administration of 2 Gm. of choline chloride per day, proved satisfactory.

Albumin excretion in the urine was rare and, as usually observed, only slight so that the danger of significant damage to the kidneys obviously does not exist.

Finally, it is also pointed out that at the beginning of the clinical application of the thiosemicarbazone, no longer customarily in use today, hypoglycemias were observed when the daily dose was too great. These could easily be controlled by the intravenous administration of grape sugar.

### MISCELLANEOUS OBSERVATIONS

The erythrocyte sedimentation rate is an important method for following the course of tuberculosis. The fact, however, that this reaction undergoes a peculiar change under thiosemicarbazone medication not only in tuberculosis, but also in certain forms of polyarthritis, makes it appear questionable whether under thiosemicarbazone therapy this reaction still possesses its full applicability in the prevailing sense. A certain relation between the effect of Conteben upon this reaction and of the dose could be determined insofar as, with high initial doses, normal values are more frequently obtained within a few days than in the "gradual building-up" dosage generally recommended. Electrophoresis of the plasmas of tuberculous patients permitted recognition of the fact that in exudative processes an increase at the alpha-globulin predominates, while in chronic, proliferating, cirrhotic forms, the coarsely disperse globulins, that is, the fibrinogen and the gamma-globulin, increase markedly. A strong increase of the alpha-globulins is therefore interpreted as indicating progression of the disease and a marked increase of the coarsely dispersed proteins, especially of the gamma-globulins, as widening of a good defense by the host. Heilmeyer pointed out that under thiosemicarbazone treatment a typical diminution of the alpha-globulins and an increase of the gamma-globulins is obtained. This finding was also confirmed by Klee in 100 electrophoresis tests. This effect of the drug may represent an "unspecific" action, that is, an action going beyond the actual bacteriostatic effect of the Conteben upon the tuberculous infection. Further investigations must show by what mechanism this effect of thiosemicarbazone is produced.

The influence of thiosemicarbazone therapy upon the tuberculin sensitivity of the skin and the complement-binding antibodies in the blood can not yet be evaluated conclusively, in spite of wide observations. In this connection it is of interest that Heilmeyer, Schaich, and Brandtner have noted that tuberculin salves, respectively treated with Conteben, streptomycin, or para-amidosalicylic acid, give the normal positive skin reaction on rubbing the salve into the skin of tuberculin-positive patients only in the case of the streptomycin or the para-amidosalicylic acid salves. In contrast, the tuberculin salve containing Conteben gave negative results or results at least materially weaker than normal. Before carrying out the skin test on man, the tuberculin salve had to be subjected to the action of the medicament for about twenty-four hours.

SUMMARY

A review has been made of the collected experiences with Conteben (TbI/698), a substance of the thiosemicarbazone series which has been used in Germany in the treatment of over 10,000 patients with various forms of tuberculosis.

Miliary tuberculosis and tuberculous meningitis are not satisfactorily controlled by Conteben therapy.

In pulmonary tuberculosis the activity of Conteben shows itself most clearly if the lesion is associated with a perifocal inflammatory process. The more labile the lesions and the better the blood supply therein appears to be, the more promising is the thiosemicarbazone therapy. Chronic stabilized cases of pulmonary tuberculosis react, as would be expected, less satisfactorily to thiosemicarbazone medication.

Cavernous processes often respond very impressively to oral administration of the drug. Intracavernous thiosemicarbazone treatment promises success even in severe, progressive cavernous processes. Conteben has apparently proved satisfactory in the preparation of patients for operation and for controlling postoperative complications.

The best tendency toward healing has been shown by mucous membrane tuberculosis, such as: tuberculous tracheobronchitis; tuberculosis of the bronchus; and laryngeal, intestinal, and bladder tuberculosis.

The experiences with thiosemicarbazone therapy do not yet permit a final judgment of its effectiveness in renal tuberculosis, but certain of the preliminary reports are encouraging. Similarly, no final judgment is possible on the degree of response of bone and joint tuberculosis to thiosemicarbazone therapy. Tuberculosis of the soft parts, particularly with the formation of fistulas, however, may already be included among the fields where the preparation is definitely indicated.

In thiosemicarbazone therapy the dosage must be strictly individualized, i.e., it must be adapted to the form and the stage of the tuberculous process, the responsiveness of the manifestation of tuberculosis, and the respective individual tolerance of the patient. The usual daily dose of Conteben for adults amounts to approximately 2 mg. per Kg. administered by the oral route.

Thiosemicarbazone therapy is not free from toxic effects. At the beginning of the clinical tests, toxic phenomena were extensively produced because of ignorance of the most suitable dosage and the peculiarities of the mode of action of the drug. Many of these reactions are completely avoidable today within the range of the guidelines for dosage which have been tested and proved satisfactory. At the beginning of therapy, lack of appetite and gastric complaints are not rare. These phenomena usually disappear in spite of continuation of the administration of the drug. Exanthemata, which are frequently preceded by conjunctivitis, have been observed.

Within the range of the dosage now recommended, anemias are relatively rare, but in larger doses (300 mg. per day or more) they are more frequent and are hemolytic in type.

Agranulocytosis and granulocytopenia during the course of thiosemicarbazone therapy have been observed. Consequently, it is essential that all patients on

thiosemicarbazone therapy be carefully observed for the possible occurrence of this reaction.

The effect of Conteben therapy upon the liver function has not yet been determined unequivocally. Under thiosemicarbazone therapy the more or less strongly marked tendency in tuberculosis toward the development of a fatty liver may occur to an increased degree. This process is apparently reversible and, in a few instances, could no longer be detected laparoscopically ten to twelve weeks after discontinuing the medication.

SUMARIO

*Estado Actual de la Quimioterapia de la Tuberculosis con Contepén, Sustancia de la Serie de la Tiosemicarbazona. Repaso*

Este repaso comprende las observaciones compiladas acerca de Contebén (TbI/698), sustancia de la serie de la tiosemicarbazona utilizada en Alemania en el tratamiento de más de 10,000 enfermos con varias formas de tuberculosis.

La granulia y la meningitis tuberculosa no fueron cohibidas satisfactoriamente con la Contebenoterapia.

En la tuberculosis pulmonar la actividad de Contebén se manifiesta más netamente si la lesión se asocia a un proceso inflamatorio crónico. Mientras más lábiles las lesiones y mejor parezca ser la circulación en las mismas, más prometedora resulta la tiosemicarbazonoterapia. Los casos estabilizados, crónicos de tuberculosis pulmonar reaccionan, según era de esperar, menos satisfactoriamente a dicha medicación.

Los procesos cavernosos responden a menudo en forma muy imponente a la administración oral de la droga. La tiosemicarbazonoterapia intracavernosa promete éxito hasta en los procesos cavernosos evolutivos graves. El Contebén ha aparentemente resultado satisfactorio para la preparación de los enfermos para operaciones y para cohibir complicaciones postoperatorias.

La mejor tendencia hacia la curación fué observada en las tuberculosis de las mucosas, tales como: tráqueobronquitis tuberculosa; y tuberculosis bronquial, laríngea, intestinal y vesical.

Las observaciones realizadas con la tiosemicarbazonoterapia no permiten pasar todavía juicio definitivo acerca de su eficacia en la tuberculosis renal, pero son alentadores algunos de los informes preliminares. Así también, no es posible expresar juicio definitivo con respecto al grado de respuesta de la tuberculosis ósea y articular a la tiosemicarbazonoterapia. Sin embargo, ya cabe incluir entre los campos en que la preparación está claramente indicada la tuberculosis de los tejidos blandos, en particular si hay fístulas.

En la tiosemicarbazonoterapia, hay que individualizar absolutamente la posología, es decir, hay que adaptarla a la forma y el estado del proceso tuberculoso, in susceptibilidad de las manifestaciones tuberculosas y la tolerancia individual del enfermo. La dosis diaria habitual de Contebén para personas adultas es de unos 2 mg. por kg. de peso.

La tiosemicarbazonoterapia no está exenta de efectos tóxicos. Al comenzar las

pruebas clínicas, observáronse fenómenos tóxicos en gran escala debido a no conocerse la posología más apropiada y a las peculiaridades del modo de actuar de la droga. Muchas de esas reacciones son completamente evitables hoy día rigiéndose por las guías posológicas que, después de comprobadas, han resultado satisfactorias. Al iniciar la terapéutica, no es raro notar anorexia y síntomas gástricos, pero esos fenómenos suelen desaparecer, aun continuando la administración de la droga. Además, se han observado exantemas, frecuentemente precedidos de conjuntivitis.

Dentro de los límites de la posología recomendada actualmente, las anemias son relativamente raras, pero con dosis mayores (300 mg. por día o más) son más frecuentes y toman forma hemolítica.

Se han observado agranulocitosis y granulocitopenia durante la tiosemicarbazonoterapia, por lo cual es indispensable la observación cuidadosa de todos los enfermos que la reciban para descubrir esa reacción, si se presenta.

No se ha determinado todavía positivamente el efecto de la contebenoterapia sobre la función hepática. Con la tiosemicarbazonoterapia puede acentuarse la tendencia más o menos poderosa que existe en la tuberculosis a degeneración adiposa del hígado. Este proceso es aparentemente reversible y, en algunos casos, no podía ser ya observado laparoscópicamente de diez a doce semanas después de haberse suspendido la medicación.

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# THE IMPLICATIONS OF CHANGING MORBIDITY AND MORTALITY RATES FROM TUBERCULOSIS[1, 2]

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## INTRODUCTION

The war years have left an indelible mark on our civilization. There have been dramatic and tremendous advances in science and technology. Man has been unable to keep up with these advances in making the application indicated for his advancement and improvement. The vast possibilities of atomic energy still fluctuate between the powers for life or death, as do also man's heroic efforts to unite for peace.

Our advances in the medical sciences have been enormous in recent years. Some diseases definitely can be brought within control; their eradication on a world-wide scale awaits only the funds and the personnel needed to apply the known measures. The ravages of other diseases have been substantially reduced by the newer methods of antimicrobial therapy, but there remain many which we are still unable to prevent fully or to treat effectively.

As measured by the declining death rates, tuberculosis would appear to be nearing the controllable state, but we may ask if this favorable decline is as significant as it seems. In the years between 1940 and 1947 the number of deaths from tuberculosis in the United States declined 20 per cent. However, in the same period the new reported cases rose 33 per cent; moreover, we know that the known cases are perhaps only half of the problem that really exists. Is it not time that we raise our sights from the cemeteries and the premature graves to the living tuberculous who really need our attention and for whom we can still do something? It must be obvious that so long as the number of new cases remains constant or, worse, increases, this scourge of mankind is not only not under control, but is in fact getting out of control.

Therefore, if we are to have an idea of the situation facing us now and in the near future, it is most timely to look closely at whatever official records are available on tuberculosis mortality and, especially, morbidity in recent years. For this purpose let us review the trend during the fast-moving years of the present decade.

## CHANGES IN DEATH RATES[3]

In 1940 the tuberculosis death rate in the United States was 45.8 per 100,000 population; in 1947 it had fallen to 33.5, a decline of 27 per cent (figure 1). If

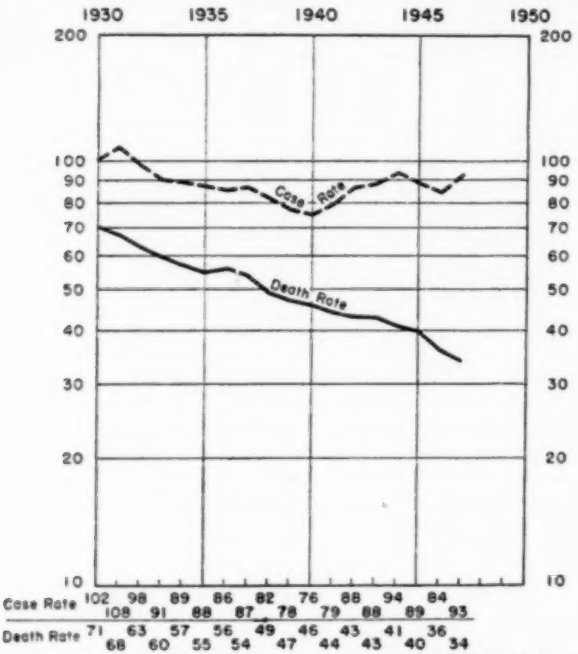
[1] From the New York Tuberculosis and Health Association.

[2] Presented before the Medical and Public Health Sections Joint Session, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 3, 1949.

[3] All rates here are based on deaths according to place of occurrence; in the opinion of the authors, this method of determination is most useful for administrative purposes: hospitalization, examination of contacts, follow-up, and so on.

we consider the individual states as units, every section of the country, to a greater or lesser extent, reported declines in the tuberculosis death rate, except South Dakota in which there was a nominal increase in the "recorded" death rate. If we group certain states into familiar divisions, we find in New England a decline of 16 per cent in the death rate during the period 1940–1947; in the Middle Atlantic states, a decline of 21 per cent; in the East North-Central states, 26 per cent; in the West North-Central states, 24 per cent; in the South

Tuberculosis Morbidity and Mortality Rates* in the United States since 1930




*Per 100,000 population for new cases registered annually, according to National Tuberculosis Association and for deaths recorded by National Office of Vital Statistics.
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Atlantic states, 30 per cent; in the East South-Central states, 28 per cent; in the West South-Central states, 32 per cent; in the Mountain states, 24 per cent; and in the Pacific states, 36 per cent.[4]

Should we want to estimate the probable tuberculosis death rate in the near future, the likelihood is that in 1950 the tuberculosis death rate for the country as a whole will be considerably under 30 per 100,000. But this would be only an

[4]Reprints of the paper, available from the authors, contain complete tables of the data for each state.

average, since in certain places it would be even lower, while in others it will be years before that level is reached. In 1947, a tuberculosis death rate as low as 11.3 per 100,000 was recorded in the state of Utah, whereas in nearby Arizona the death rate was 118.6. It must be remembered, however, that Arizona is still sought by health seekers and that its own population is made up of a number of inhabitants of Spanish and Indian origin. The most populous state in the Union, New York, had a death rate of 37.9; but in its midst, the Borough of Manhattan, New York City, with a population as great as that of the entire state of Kansas or of South Carolina, had a rate of 73.

However, is the tuberculosis death rate, especially now, a measure of the tuberculosis situation? The answer is definitely "no." The time is past when community programs for the control of the disease and, more particularly, the facilities and measures required for the fight against it—hospitals, clinics, laboratory service, case-finding surveys, home follow-up, and health education campaigns—are to be determined on the basis of those already dead. What matters most today are those patients currently stricken and the remaining general population for which effective preventive measures must be further developed.

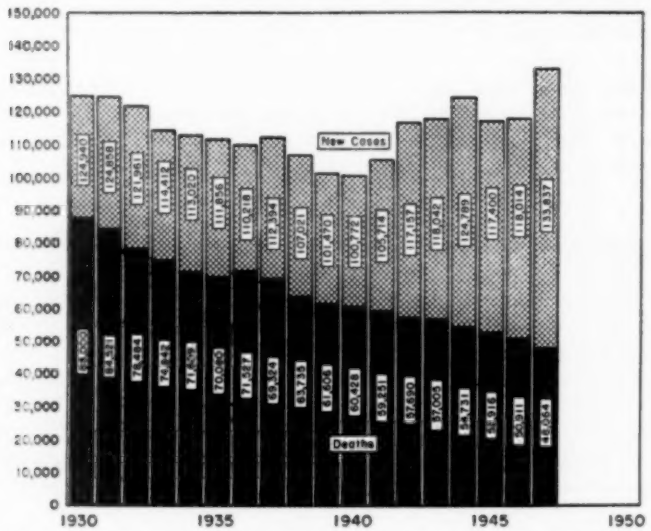
## CHANGES IN MORBIDITY

The registration of new cases of tuberculosis offers a much more timely and useful index of the present tuberculosis problem than does the death rate. In 1940, according to reports from state health departments, 100,772 new cases of tuberculosis were registered in the United States. The morbidity rate thus was 76.4 per 100,000 population (figure 2). In contrast with a decline in the number of tuberculosis deaths from 60,428 to 48,064 between 1940 and 1947, a total of 133,837 new cases was registered by health authorities in 1947, an increase of 33,065 cases over the 1940 number. It will be said that this advance must have been due primarily to the increasing and widespread use of roentgenographic examinations, particularly in mass surveys. But such an observation ignores the fact that mere growth of population brought its own tuberculosis cases and that during the war years the migration of workers to industrial centers exposed them to new risks and hardships—overtime work, inadequate housing, and increased congestion. Moreover, lately there has been an increasing flow into the United States of people, such as Puerto Ricans and displaced persons, who are all liable to suffer a higher incidence of tuberculosis than the acclimated stocks. Surveys have undoubtedly played a part in the reported increase. This factor cannot detract from the cold fact that we now have on our hands a larger number than ever of known cases of tuberculosis. Another factor to be considered is that there has not been a uniform practice in regard to the determination of tuberculosis cases. This was truer perhaps at the beginning of the mass roentgenographic surveys, for there is gradually developing a much better understanding of the need for follow-up and re-examination of suspects first discovered on initial roentgenograms.

The extent to which mass chest X-ray surveys account for the reported increase of tuberculosis is, perhaps, overestimated. We are told that in New York

City, where more than 500,000 roentgenographic examinations for tuberculosis are recorded annually, such examinations were responsible for adding only 3.4 per cent to the new cases registered in 1947 (1). This observation is further confirmed by the fact that, in the same community, a classification of the newly registered cases by stage of disease reveals, not an increasing proportion found in the early or minimal stage but, rather, more in the advanced stages than was true a few years ago (2). In 1943, 66 per cent were found to be in either the second or third stage; in 1948, 76 per cent were so classified.

Tuberculosis Cases and Deaths Reported in the United States since 1930




Figures by courtesy of National Tuberculosis Association and the National Office of Vital Statistics.
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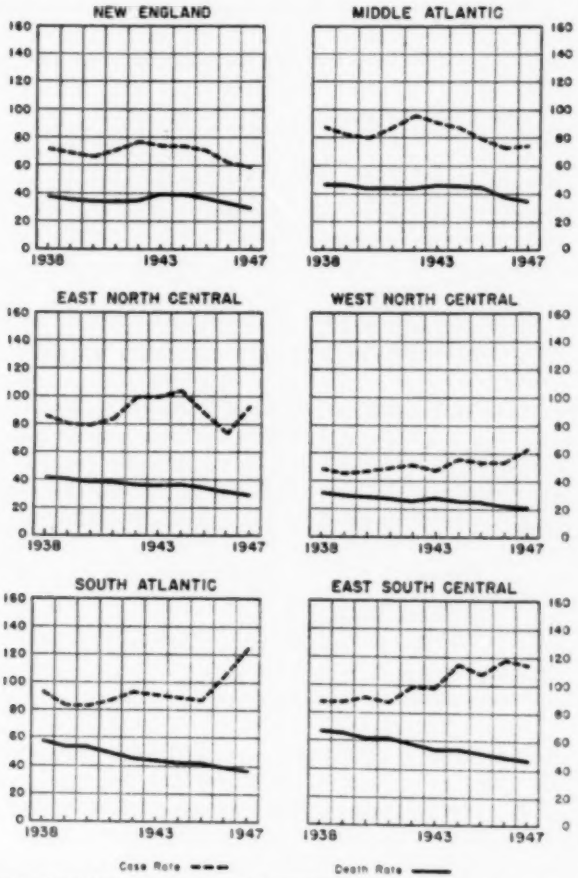
Available figures on another large center of population, namely, Los Angeles, show that even in 1948 only 13.2 per cent of the newly reported cases were in the minimal stage; the remainder, or 86.8 per cent, were advanced cases. More than one-half of all the new cases in Los Angeles during the past three years have been far advanced cases. During the first quarter of 1949, almost a 50 per cent increase in the reported cases was registered, compared with those first reported during the same period for 1948 (3). Let it also be recalled that in certain states a high proportion of all newly reported cases is comprised of those identified only at the time of death by means of a death certificate. According to state health department reports, in one instance the percentage of new cases reported in this manner constituted 80 per cent of the total. Finally we must realize that the complete tuberculosis roster in a community should include not only new

cases registered within a given twelve months, but also records of the patients who were previously reported and who have not yet recovered or died. It is obvious, therefore, that the available figures on new cases only are an understatement of the present tuberculosis situation.

Tuberculosis Morbidity and Mortality Rates* in Various Divisions of the United States, 1938 to 1947




*New cases registered and deaths recorded per 100,000 population.

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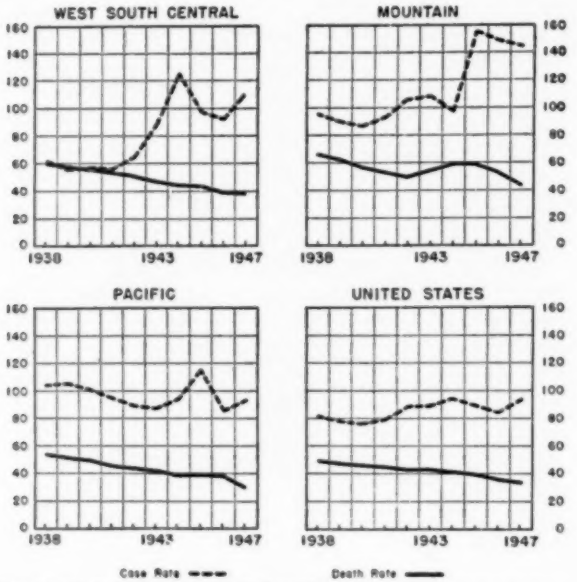
Since such complete tuberculosis rosters are not readily available, it is worthwhile and necessary to study the number of new cases registered during the period under consideration. Although, between 1940 and 1947, the population of the

United States increased from 131,669,275 to 143,414,000, an increase of 11,744,725, the tuberculosis morbidity rate for new cases alone rose 22 per cent from 76.4 to 93.3 per 100,000.

In the New England section the morbidity rate declined 12 per cent from 66.9 in 1940 to 59.2 in 1947. In the three Middle Atlantic states, there was a decrease of 7 per cent in the morbidity rate during the 1940–1947 period, namely, from 79.6 to 74.1. In the East North-Central division, encompassing the area from Ohio to Wisconsin, the tuberculosis morbidity rate rose from 79.6 to 93.4,

Tuberculosis Morbidity and Mortality Rates* in Various Divisions of the United States, 1938 to 1947




*New cases registered and deaths recorded per 100,000 population.

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an increase of 17 per cent. In the West North-Central division, from Kansas to Minnesota, the morbidity rate went up from 47.3 to 62.7, or 33 per cent. In the South Atlantic states, from Delaware down to Florida, there was an increase in the registration rate of new cases of tuberculosis from 82.9 to 123.7, a rise of 49 per cent. Even greater was the increase in the four West South-Central states, which include Texas, the rate rising from 56.6 to 111.2, or 96 per cent. In the Mountain states, Montana to Nevada, the rate rose from 86.6 to 144.9, an increase of 67 per cent. In the Pacific states, the already high morbidity rate of 101.3 in 1940 came down to 93.0 in 1947, a decline of 8 per cent. As previously stated, for the country as a whole the registration rate for new cases of tubercu-

losis rose from 76.4 to 93.3, or 22 per cent, while the death rate was declining from 45.8 to 33.5, or 27 per cent (figures 3 and 4).

### NEW CASES

Since it is primarily with the recently reported tuberculous individuals, most of them presumably still living, with whom we are at present most concerned, let us examine their actual number and determine how it compares with that of a few years ago. In the New England division the number of new cases reported in 1947 totalled 5,412, which is 225, or 4 per cent, less than the 5,637 reported in 1940. Nevertheless, the percentage of decline in the number of cases was only half that in the number of deaths, which was 9 per cent. Moreover, the decline in this area was not general, for both in Vermont and in Rhode Island there were more new cases registered in 1947 than in 1940.

In the all important three states in the Middle Atlantic division—New York, New Jersey, and Pennsylvania—a total of 21,709 new cases was registered in 1947, a number which is, however, 215 fewer, or 1 per cent less, than that in 1940 when 21,924 cases were reported. While the number of new cases remained practically constant in these three states, the number of deaths was reduced by 17 per cent.

In the East North-Central division, the number of new cases rose from 21,205 in 1940 to 27,307 in 1947, an increase of 6,102. During this same period the number of deaths in this section declined 19 per cent, whereas the registration of new cases was higher by 29 per cent.

In the West North-Central division, where the number of deaths decreased 23 per cent between 1940 and 1947, the number of new cases registered rose 34 per cent, from 6,399 in 1940 to 8,599 in 1947. Even in Iowa, where the death rate decreased 33 per cent from 17.1 in 1940 to 11.8 in 1947, the number of new cases registered increased by 14 per cent, namely, from 589 in 1940 to 670 in 1947. As a matter of fact, throughout the entire West North-Central section, the death rate in 1947 was only 21.7, a rate 24 per cent lower than that in 1940. However, the number of new cases of tuberculosis in 1947 (8,599) was higher in each state than it had been in 1940. Consequently, it may be seen that there is as much known tuberculosis requiring attention in that area as ever; in fact, the situation is not yet under control.

In the South Atlantic division, ranging from Delaware to Florida, where the number of tuberculosis deaths decreased by 24 per cent between 1940 and 1947, the number of new cases registered rose 61 per cent during those years, from 14,850 to 23,866, an increase of 9,016. In that group, which includes eight states and the District of Columbia, the number of deaths increased only in Delaware (by 2 per cent) but the number of new cases in 1947 was higher in every one of those states than it had been in 1940.

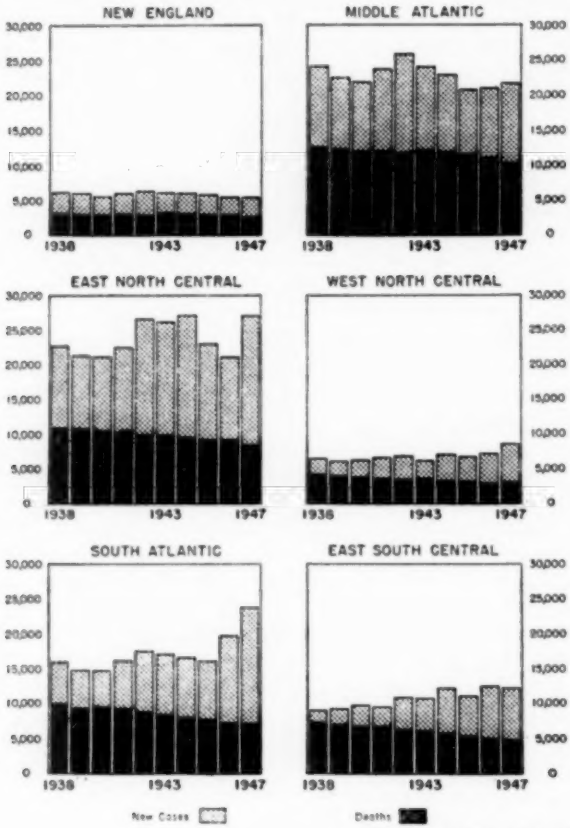
In the four East South-Central states, the deaths declined 28 per cent, but the number of new cases rose from 9,766 to 12,431, or 27 per cent.

In the West South-Central group of four states, which includes Texas, the

deaths there, too, were 28 per cent fewer than in 1940, but the number of new cases reported in 1947, 15,396, was double that in 1940, which was 7,399.

In the Mountain states, where the population is not very large, the number of tuberculosis deaths decreased by 20 per cent, but the number of new cases increased 76 per cent.

Tuberculosis Cases (New) and Deaths in Various Divisions of the United States, 1938 to 1947

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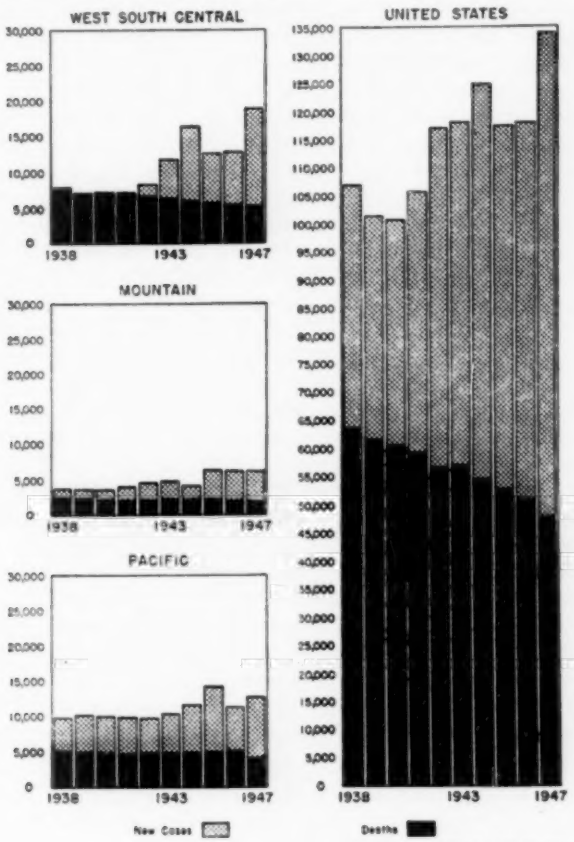
In the three Pacific states, a similar dissociation of the trend of mortality from that of morbidity was noted, the deaths being 11 per cent fewer, whereas the new cases rose in number from 9,966 to 12,751, or 28 per cent. The difference between mortality and morbidity trends is especially striking in California where we have the spectacle of the tuberculosis death rate declining by 37 per cent,

from 55.7 to 35.2 between 1940 and 1947 and, on the other hand, an actual increase in the number of new cases from 7,807 to 9,309, or a rise of 19 per cent. This increase was due in great part, of course, to the notable increase in population which occurred during the World War II years. The fact remains, however,

Tuberculosis Cases (New) and Deaths in Various Divisions of the United States, 1938 to 1947

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that in that large area there are actually more tuberculous patients requiring care than ever before.

The picture revealed by these changing rates of tuberculosis mortality and morbidity for the United States as a whole is a sharp reflection of the fact that, while the deaths from tuberculosis declined from 60,428 in 1940 to 48,064 in 1947, a reduction of 20 per cent, new reported cases actually rose from 100,772 to

133,837, an increase of 33,065. To all those engaged in the fight against tuberculosis, this situation presents an even greater problem in control than that which previously existed (figures 5, 6).

## SITUATION IN 1948

Complete reports for the year 1948 are not yet available. However, the amount of information at hand is sufficiently representative to indicate the current extent of the problem and to confirm the continuing trends of a decline in mortality and an increase in the number of known cases of tuberculosis.

In fifteen[5] of the largest cities of the United States, preliminary provisional reports obtained by courtesy of the local health authorities show that, within this group of communities with a total population of twenty-five million, 10,706 deaths from tuberculosis were recorded within their municipal limits in 1947 and 9,964 in 1948. Their death rate, therefore, fell from 43 to 39 per 100,000 population, a reduction of almost 10 per cent. Nevertheless, here also the new cases registered rose from 31,887 in 1947 to 35,242 in 1948. On the basis of cases registered in 1948, the morbidity rate was 139 per 100,000 in these important cities, compared to a rate of 93.3 for the United States as a whole during 1947. It is obvious, therefore, that the great centers of population are faced with an urgent need for additional tuberculosis hospital facilities. At this time of high building costs, this is a serious problem.

Similarly conclusive are advance reports for seventeen[6] of the more populous states with a total population of 100,571,000 in 1948. Within these states, 34,460 deaths from tuberculosis were recorded in 1947 and 31,078 in 1948; the death rate, therefore, dropped from 35 to 31 per 100,000. Of greater importance, however, is the fact that, at the same time, the number of new cases of tuberculosis registered rose from 89,767 in 1947 to 94,986 in 1948, an increase of 5 per cent. Obviously, the final nationwide reports for 1948[7] will only emphasize the different trends of the two rates.

For every tuberculosis death in the community, there are probably ten active cases in the general population. The present registration of new cases alone is revealing three times the number of deaths. It is manifest that before tuberculosis can be eradicated available facilities must be related to all the known cases of tuberculosis, old and new, rather than to the number whose lives were not saved.

[5] New York, Chicago, Philadelphia, Los Angeles, Detroit, Baltimore, Cleveland, Washington, D. C., San Francisco, St. Louis, Boston, Pittsburgh, Milwaukee, Buffalo, and New Orleans.

[6] California, Georgia, Illinois, Indiana, Kentucky, Maryland, Massachusetts, Michigan, Missouri, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Texas, Wisconsin.

[7] Just before publication, provisional reports for the entire United States for the year 1948 became available through the courtesy of the state departments of health and the National Tuberculosis Association. They showed that tuberculosis deaths that year numbered 43,529, compared with 48,064 in 1947, and that the number of new cases registered was 145,131 in 1948 compared to 133,837 in 1947.

SUMMARY

1. A widening gap is developing between the tuberculosis morbidity and mortality rates in the United States.

2. Between 1940 and 1947 the tuberculosis death rate declined from 45.8 to 33.5 per 100,000, or 27 per cent, while the registration rate of new cases rose from 76.4 to 93.3 per 100,000, an increase of 22 per cent.

3. During the period 1940–1947, the actual number of deaths fell from 60,428 to 48,064, or 20 per cent, but the number of new cases reported went up from 100,772 to 133,837, an increase of 33,065, or 33 per cent.

4. Case-finding surveys, growth of population, wartime strain, and immigration of new susceptible groups have all contributed to a larger number of known tuberculosis cases. At the same time, extension of hospital facilities, abolition of the "means test" in certain areas, and widespread health education campaigns have resulted in a larger number of patients accepting hospitalization. Modern treatment of the disease, including rest, collapse therapy, surgery, and antimicrobial therapy, is increasingly reducing the mortality though not necessarily preventing the outbreak of new cases.

5. (a) The death rate from tuberculosis is a limited and inadequate index of the prevalence of the disease in the community.

(b) Repeated revision of the ratio of required hospital beds to the number of deaths—first, one bed for each annual death, then, two; and now, three—reveals its inadequacy.

(c) The number of known, active cases is the proper basis for estimating required facilities. Hospital beds are needed for those stricken and not for the dead.

SUMARIO

*Connotaciones en los Cambios en las Tasas de Morbidad y Mortalidad Tuberculosas*

1. Una separación cada vez mayor entre las tasas de morbidad y mortalidad tuberculosa va tomando forma en los Estados Unidos.

2. Entre 1940 y 1947 la mortalidad tuberculosa disminuyó de 45.8 a 33.5 por 100,000, o sea en 27 por ciento, en tanto que el coeficiente de inscripción de nuevos casos se elevó de 76.4 a 93.3 por 100,000, o sea un aumento de 22 por ciento.

3. Durante el período 1940–1947, el número de muertes bajó de 60,428 a 48,064, o sea en 20 por ciento, pero el numero de casos denunciados subió de 100,772 a 133,837, o sea un aumento de 33,065 (33 por ciento).

4. Las encuestas para descubrimiento de casos, el crecimiento de la población, los esfuerzos de la guerra y la inmigración de nuevos grupos susceptibles, todo esto ha contribuído a acrecentar el número de casos conocidos de tuberculosis. Al mismo tiempo, la ampliación de los medios hospitalarios, la abolición de las "pruebas de pobreza" en ciertas zonas y la generalización de las obras pro educación sanitaria han hecho que un número mayor de enfermos acepte la hospitalización. El moderno tratamiento de la dolencia, comprendiendo reposo,

colapsoterapia, cirugia y terapéutica antimicrobiana, va rebajando continuamente la mortalidad, pero no impidiendo forzosamente la aparición de casos nuevos.

5. (a) El coeficiente de mortalidad tuberculosa constituye un índice limitado e inadecuado de la frecuencia de la enfermedad en la colectividad.

(b) Así lo revela la repetida revisión de la proporción de camas de hospital que se necesita por número de muertes: primero, una cama por cada muerte anual; después dos; y ahora, tres.

(c) El número de casos activos, conocidos ofrece la base apropiada para calcular las camas que se necesitan. Esas camas se necesitan para los dolientes y no para los muertos.

*Acknowledgment*

With appreciative acknowledgment of the helpful assistance given by A. M. Lowell in the preparation of the tabulations.

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# PREVALENCE OF CLINICALLY SIGNIFICANT PULMONARY TUBERCULOSIS AMONG INMATES OF NEW YORK STATE PENAL INSTITUTIONS[1]

JULIUS KATZ AND ROBERT E. PLUNKETT

(Received for publication May 19, 1949)

## INTRODUCTION

While there is an impression among phthisiologists that the prevalence of clinically significant pulmonary tuberculosis among inmates of correctional institutions is higher than in the general population, search of the literature on the subject reveals few specific data with which to substantiate this impression.

The report of the American Trudeau Society Committee on Tuberculosis Control in Penal Institutions (1) mentions the results of case-finding surveys in two of California's state prisons. A total of 4,415 inmates were examined, with a prevalence rate of 1.7 per cent. The report indicates that a similar rate was obtained among prison inmates in the state of Washington.

Bettag (2) reported a prevalence rate of 0.89 per cent active tuberculosis among 3,113 prisoners, and stated that "This is a morbidity rate of 899 per 100,000, or seven times greater than for the state of Illinois." Garry (3) reported a case-finding study among inmates and employees of two penal and two correctional institutions for males in Ohio, using 35 mm. films. Patients showing roentgenographic evidence suggesting tuberculosis were classified only as "suspected tuberculosis," since "the survey was conducted primarily as a screening project and recommendations were made for diagnostic follow-up in those cases where it was indicated." Among inmates, 3.3 per cent were considered to have "suspected tuberculosis."

From 1944 through 1948, chest roentgenographic surveys were conducted among inmates of all institutions of the New York State Department of Correction. This department administers fifteen institutions, consisting of seven prisons, three reformatories, three institutions for mentally defective delinquents, and two hospitals for insane prisoners. Convicted criminals are assigned to these institutions according to sex, age, mental condition, and type of crime. The total average daily inmate population for 1946 was 14,531. For administrative reasons, roentgenographic examination was not made compulsory, so that only about 89 per cent of the inmates were examined. Standard 14 by 17 films were used in three institutions, while 70 mm. films were used in the other twelve. All final diagnoses were made from 14 by 17 films.

## RESULTS

*Total prevalence rates:* The prevalence of clinically significant pulmonary tuberculosis among inmates of the individual institutions is shown in table 1.

[1]From the Division of Tuberculosis Control, New York State Department of Health, Albany, New York.

TABLE 1

*Prevalence of Clinically Significant Tuberculosis among Inmates of the Institutions of the New York State Department of Correction*

| INSTITUTION AND YEAR OF SURVEY | TOTAL NUMBER INMATES X-RAYED | CASES OF CLINICALLY SIGNIFICANT TUBERCULOSIS | |
|---|---|---|---|
| | | Number | Per cent |
| *Males* | | | |
| A. Reformatories | | | |
| Coxsackie 1944 | 617 | 3 | 0.5 |
| Elmira 1948 | 1,511 | 3 | 0.2 |
| Total | 2,128 | 6 | 0.3 |
| B. Institutions for mental defectives | | | |
| Napanoch 1948 | 907 | 2 | 0.2 |
| Woodbourne 1947 | 615 | 12 | 2.0* |
| Total | 1,522 | 14 | 0.9 |
| C. Prisons | | | |
| Attica 1948 | 1,862 | 11 | 0.6 |
| Auburn 1948 | 1,161 | 3 | 0.3 |
| Clinton 1947 | 1,758 | 56 | 3.2* |
| Great Meadow 1948 | 686 | 5 | 0.7 |
| Sing Sing 1948 | 1,697 | 16 | 0.9 |
| Wallkill 1948 | 377 | 1 | 0.3 |
| Total | 7,541 | 92 | 1.2 |
| D. Hospitals for criminal insane | | | |
| Dannemora 1948 | 1,052 | 25 | 2.4 |
| Matteawan 1948 | 1,166 | 20 | 1.7 |
| Total | 2,218 | 45 | 2.0 |
| Total male inmates | 13,409 | 157 | 1.2 |
| *Females* | | | |
| Institution for mental defectives | | | |
| Albion 1944 | 319 | 5 | 1.6 |
| Reformatory and prison | | | |
| Westfield State Farm and Womens Prison 1948 | 569 | 2 | 0.4 |
| Hospital for Criminal Insane | | | |
| Matteawan 1948 | 131 | — | — |
| Total female inmates | 1,019 | 7 | 0.7 |

* See text for explanation of these prevalence rates.

Among male inmates, the total rate was 1.2 per cent. The rates were 0.3 per cent among reformatory inmates, 0.9 per cent among mentally defective delinquents, 1.2 per cent among prison inmates, and 2.0 per cent among the criminal

insane. The rate of 1.9 per cent at the Woodbourne Institution for Male Defective Delinquents is not representative of the actual prevalence rate among inmates of this institution, since 7 of the 12 cases of tuberculosis were originally received by transfer from the other institution for mentally defective delinquents. Similarly, the rate of 3.2 per cent found in Clinton Prison is not an in-

TABLE 2

*Prevalence of Clinically Significant Pulmonary Tuberculosis among Male Inmates of the Institutions of the New York State Department of Correction By Age and Type of Institution*

| AGE | TOTAL | | | REFORMATORIES | | | INSTITUTIONS FOR MENTALLY DEFECTIVE DELINQUENTS | | | PRISONS | | | HOSPITALS FOR CRIMINAL INSANE | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number X-rayed | Number cases TB | Rate per cent | Number X-rayed | Number cases TB | Rate Per cent | Number X-rayed | Number cases TB | Rate per cent | Number X-rayed | Number cases TB | Rate per cent | Number X-rayed | Number cases TB* | Rate per cent |
| 15 to 24 | 3,949 | 23 | 0.6 | 1,957 | 6 | 0.3 | 527 | 2 | 0.4 | 1,332 | 15 | 1.1 | 133 | — | — |
| 25 to 44 | 6,492 | 78 | 1.2 | 169 | — | — | 747 | 8 | 1.1 | 4,728 | 56 | 1.2 | 848 | 14 | 1.6 |
| 45 to 64 | 2,441 | 46 | 1.9 | | | | 216 | 4 | 1.9 | 1,286 | 19 | 1.5 | 939 | 23 | 2.4 |
| 65 and over | 390 | 9 | 2.3 | | | | 30 | — | — | 105 | 2 | 1.9 | 255 | 7 | 2.7 |
| Total..... | 13,272 | 156 | 1.2 | 2,126 | 6 | 0.3 | 1,520 | 14 | 0.9 | 7,451 | 92 | 1.2 | 2,175 | 44 | 2.0 |

* One case of tuberculosis was diagnosed among 137 patients whose ages were not recorded.

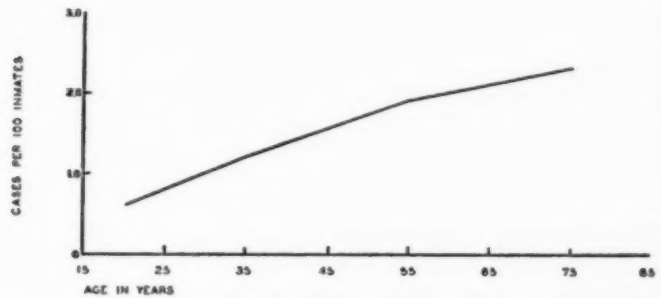


FIG. 1. Prevalence of clinically significant pulmonary tuberculosis among male inmates of all institutions of New York State Department of Correction.

dex of the prevalence rate in that institution, since this prison serves as a center for the segregation of tuberculous inmates from other institutions of the department.

The total prevalence rate among female inmates was 0.7 per cent. Because of the small number of individuals involved, the rates for the prison for women,

the Westfield State Farm (reformatory), Albion (mental defectives), and Matteawan (criminal insane) were not calculated separately.

*Prevalence rates by age:* The variation in total prevalence rates among male inmates of the different types of institutions probably results, in part at least, from differences in age distribution of the populations. Only 7.9 per cent of male

TABLE 3

*Prevalence of Clinically Significant Pulmonary Tuberculosis Among Male Inmates of Nine Institutions* of the New York State Department of Correction By Age and Color*

| AGE | WHITE | | | NON-WHITE | | |
|---|---|---|---|---|---|---|
| | Number X-rayed | Number cases TB | Rate per cent | Number X-rayed | Number cases TB | Rate per cent |
| Total | 6,158 | 94 | 1.5 | 3,047 | 30 | 1.0 |
| 15 to 24 | 1,343 | 11 | 0.8 | 914 | 7 | 0.8 |
| 25 to 44 | 3,312 | 50 | 1.5 | 1,701 | 17 | 1.0 |
| 45 to 64 | 1,317 | 30 | 2.3 | 404 | 5 | 1.2 |
| 65 and over | 186 | 3 | 1.6 | 28 | 1 | 3.6 |

* Includes Vocational Institution, Napanoch, Woodbourne, Attica, Auburn, Clinton, Sing Sing, Wallkill, and Dannemora.

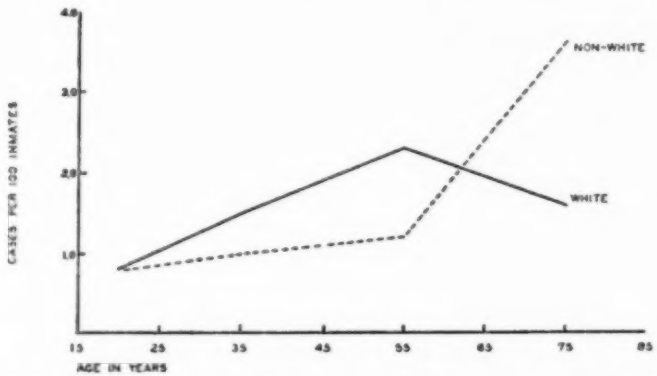


FIG. 2. Prevalence of clinically significant pulmonary tuberculosis among male inmates of nine institutions of New York State Department of Correction—by age and color.

reformatory inmates were over twenty-five years of age, while 65.3 per cent of inmates of institutions for mentally defective delinquents, 82.1 per cent of prison inmates, and 93.9 per cent of criminal insane were over that age. The prevalence rates increase progressively with age in the four types of institutions. Table 2 and figure 1 show the relationship of prevalence rate to age.

Because of the small number of female inmates, prevalence rates by age were not calculated.

*Prevalence rates by race:* Age-specific prevalence rates were computed for white and non-white male inmates of nine institutions for which this information was available (table 3). The total rate was 1.5 per cent among white inmates and 1.0 per cent among the non-white. The rates were essentially the same for both groups among inmates of the reformatory and the institutions for mental defectives, but white inmates of prisons and of hospitals for criminal insane had higher rates than the Negro inmates.

Figure 2 shows no difference in prevalence rates among whites and non-whites at ages 15 to 24. Between 25 and 64 years, the rates were higher among white inmates. At 65 and over, the rates were higher among non-whites. In the last age group, however, the total number of individuals was small and the difference in rate is not significant.

TABLE 4

*Distribution of Clinically Significant Pulmonary Tuberculosis Among Male Inmates of Nine Institutions of the New York State Department of Correction By Race and Stage of Disease**

| STAGE | TOTAL | | WHITE | | NON-WHITE | |
|---|---|---|---|---|---|---|
| | Number | Per cent | Number | Per cent | Number | Per cent |
| Minimal | 61 | 49.2 | 46 | 49.0 | 15 | 50.0 |
| Moderately advanced | 47 | 37.9 | 38 | 40.4 | 9 | 30.0 |
| Far advanced | 16 | 12.9 | 10 | 10.6 | 6 | 20.0 |
| Total | 124 | 100.0 | 94 | 100.0 | 30 | 100.0 |

* Includes New York State Vocational Institution, Napanoch and Woodbourne Institutions for Defective Delinquents, Attica, Auburn, Clinton, Sing Sing (952 inmates), and Wallkill Prisons, and Dannemora State Hospital.

*Stage of disease:* Among the 164 cases diagnosed, 48.8 per cent were in the minimal stage, 35.9 per cent moderately advanced, and 15.3 per cent far advanced at the time of diagnosis. Among the 124 patients for whom information regarding race was available, the percentage in the minimal stage was essentially the same for white as for non-white patients. The percentage of cases of moderately advanced tuberculosis was somewhat higher among white inmates, while that of far advanced disease was higher among non-white inmates, as shown in table 4.

## COMMENT

The prevalence rate of 1.2 per cent clinically significant tuberculosis found among male inmates in this study is considerably higher than in the general population, among whom the rate is estimated to be about 0.3 per cent. The higher rate among inmates of this type of institution indicates the need for tuberculosis control programs not only for the care of tuberculous inmates, but also for the protection of nontuberculous inmates and employees. These programs should include: (*1*) initial roentgenographic examinations and periodic resurveys of the total inmate and personnel population of each institution; (*2*) provision

for the segregation and treatment of inmates with clinically significant tuberculosis; (3) routine roentgenographic examination of all inmates upon admission and of all prospective employees.

A program to include these services is being developed for all institutions of the New York State Department of Correction.


## SUMMARY

1. Chest roentgenographic surveys were conducted in all fifteen institutions of the New York State Department of Correction. A total of 14,428 inmates were examined.

2. The prevalence of clinically significant pulmonary tuberculosis among male inmates was 1.2 per cent, among females 0.7 per cent.

3. The prevalence rates were higher in the older age groups. The rates were higher among white inmates than among non-white.

4. The high prevalence rates indicate the need for control programs in these institutions.

## SUMMARIO

*Frecuencia de la Tuberculosis Pulmonar Clínicamente Significativa entre los Presos de los Establecimientos Penales del Estado de Nueva York*

1. En las quince instituciones del Departamento de Correccion del Estado de Nueva York llevároнse a cabo encuestas radiográficas del tórax, examinándose un total de 14,428 presos.

2. La frecuencia de tuberculosis pulmonar clínicamente significativa entre los reclusos varones representó 1.2 por ciento y entre las mujeres 0.7 por ciento.

3. Las tasas fueron más altas entre los grupos de más edad y también entre los blancos que en otras razas.

4. Estos índices elevados indican la necesidad de obras antituberculosas en dichos establecimientos.



*Acknowledgment*

The authors take this opportunity to express their appreciation for the interest and cooperation of Commissioner John A. Lyons and Deputy Commissioners William E. Leonard and Paul D. McGinnis of the New York State Department of Correction.


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# POSTOPERATIVE MANAGEMENT OF THORACOPLASTY PATIENTS[1, 2]

JOHN ALEXANDER

(Received for publication May 1949)

In preparation for thoracoplasty and the postoperative period, the patients in my clinic have roentgenograms made within a week of operation so that any otherwise undetectable change in the lesions may be known. A bronchoscopic examination is made within three months of the first operative stage in all patients, but within two weeks if tuberculous bronchitis is known to have been present. If streptomycin is being given for a good reason at the time the patient is received for thoracoplasty, it is continued at least until the operations have been completed, regardless of the number of days of administration.

If the blood transfusion routinely given during the operation has not completely replaced the measured amount of blood lost, it is continued after operation, and 2,000 or 3,000 cc. of five per cent glucose solution in distilled water are slowly administered so that the output of urine for the twenty-four hours after operation is at least 1,000 cc. Oxygen is, of course, given to any patient who is even slightly dyspneic or cyanotic, or who has a rapid pulse or low blood pressure.

So-called "thoracic shock" is usually due to excessive paradoxical respiration or to too great pulmonary collapse for a single operative stage, or to both. Both are far more easily prevented by the restriction of the costal resections than combated. Paradoxical respiration may be partly controlled by snug strapping, a shot bag, the posturing of the patient so as to cause the weight of his body to steady the mobile portion of the thoracic wall, positive pressure breathing, a Drinker respirator (in extreme cases), and by relief of dyspnea, for dyspnea and paradoxical respiration are mutually aggravating. The following measures for the relief of dyspnea should be kept in mind as possibly useful in different combinations: oxygen; blood transfusion if the hemoglobin is low; aspiration of fluid or air (therapeutic or spontaneous pneumothorax, or accidental operative tear of the parietal pleura) that may be present in either pleural cavity; relief of abdominal distension; a trial of the semi-Fowler position; and, probably the most important of all, keeping the tracheobronchial tree free of secretions. This last measure is, obviously, most simply effected by frequent coughing and expectorating, with or without the aid of: (*1*) small doses of morphine to relieve pain without unduly dulling the cough reflex; (*2*) carbon dioxide inhalations to produce deep respirations and dislodgment of secretions; (*3*) support of the abnormally mobile portion of the thoracic wall by the firm pressure of a nurse's hand; (*4*) steam inhalations and expectorants; and (*5*) lying on the operated side or back with

[1] From the Section of Thoracic Surgery, Department of Surgery, University of Michigan, Ann Arbor, Michigan.

[2] Presented before the Medical Section as part of the symposium on *Surgery*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

the bed flat, "Trendelenburged," or in the Fowler position. If these measures should fail to keep the airways clear and if there should be signs of a "drowned lung" or atelectasis, aspiration of the trachea and bronchi by catheter should be carried out and, if effective, repeated as often as necessary to keep the airways clear. If catheter aspiration should fail, aspiration by bronchoscopy should be done. If dyspnea should be due to a reactivation or spread of the tuberculous lesions, streptomycin should be given promptly.

The prevention or control of scoliosis is a difficult and as yet unsatisfactorily solved problem. In a large majority of the patients it is not severe and is only slightly disabling, but in a minority it is deforming and disabling in varying degrees. We use Oatway's big sandbag to keep the head tilted toward the operated side and, after the second thoracoplasty stage, Bisgard's "postural wedge compression." These measures should, at least theoretically, be continued for many months after completion of the thoracoplasty until ambulation and specific exercises have restored the muscles that should hold the spine in a normal position. Although an orthopedic brace or spinal fusion, or both, may prevent progression of deformity, an old, established scoliosis can be improved only by special braces or wedged casts and, then, a very extensive staged fusion operation.

Ten or twelve days after each thoracoplasty stage, stereoscopic standard and Potter-Bucky roentgenograms are made and the patient begins to get out of bed and is allowed to sit in a chair for five to fifteen minutes a day. Each successive operative stage is usually performed from two to three weeks after the preceding stage, whether or not the costal periosteum has been formalinized. We do not make a definite decision before the thoracoplasty is started as to how many ribs should be resected, or how many stages will be used, or whether an anterior stage will be performed. Instead, we decide that the thoracoplasty has been completed when palpation and the roentgenograms indicate that the optimal collapse has been produced for the particular lesions, the cavity usually then being invisible. Two, three, or four weeks after the last stage the patient is returned to his sanatorium. As a "positive" sputum concentrate at this time is not necessarily a bad prognostic sign, sputum examinations need not be made until a month or two after the operation.

It is the usual practice in the sanatoriums for which we are the thoracic surgery consultants to keep thoracoplasty patients more or less strictly in bed for six months and then gradually to increase their physical activities for a year before discharge. Approximately six months later the patients, if apparently cured, are allowed to return to work. Slow conversion of the sputum or slow healing of lesions in the uncollapsed portions of either lung should, of course, extend the period of convalescence.

Patients who, some months after completion of a thoracoplasty, have a visible residual cavity and "positive" sputum may be suitable for a revision of the thoracoplasty if the collapse is unsatisfactory, or for pulmonary resection or cavity drainage, according to the particular conditions.

The problem that plagues all of us from time to time is presented by the patient who has no visible cavity, no sign of an active parenchymal lesion in

either lung, no bronchoscopic evidence of tuberculous bronchitis, no bronchiectasis in bronchograms, and consistently negative sputum concentrates but whose cultures of sputum or gastric contents are constantly or intermittently positive for tubercle bacilli. Even if tuberculous bronchitis has not been diagnosed in the past from the bronchoscopic findings or has not even been suspected from signs or symptoms, a course of streptomycin is probably indicated for such patients. If the cultures should still be positive for tubercle bacilli, the physician and patient usually have a choice of only three alternatives: indefinite isolation in a sanatorium, discharge to home, and pulmonary resection of the collapsed lobe or lung. If such a patient has fatigue, low-grade fever, and other signs or symptoms of tuberculosis activity (presumably from unhealing caseous lesions) resection is usually a wise choice. But if the patient feels and appears to be perfectly well and if he thoroughly understands, and is the sort of person who can be counted upon to observe, the measures to be taken to prevent the infection of others, I seriously doubt the propriety of our demanding that he either accept the potentially dangerous operation of resection (which does not absolutely guarantee future negative cultures) or remain in a sanatorium indefinitely, perhaps for the rest of a long life. If such a person, however, cannot be counted upon to observe the precautionary measures that will protect his family and associates from infection, I believe that resection or indefinite sanatorium residence should be the only alternatives.

# THE VALUE OF CYTOLOGICAL DIAGNOSIS OF PULMONARY MALIGNANCY[1,2]

LOUIS H. CLERF AND PETER A. HERBUT

(Received for publication May 4, 1949)

In a series of 336 cases of carcinoma of the bronchus observed in the Department of Broncho-Esophagology at the Jefferson Hospital from 1930 to 1945, the diagnosis was made in approximately 65 per cent by bronchoscopic biopsy. A follow-up of these cases showed that, although many exploratory thoracotomies were performed, few lesions were found which were suitable for surgical resection. Invariably the primary lesion either was too extensive or there was metastasis. With an apparent increase in the number of cases of carcinoma which was being observed, it appeared that diagnostic aids other than bronchoscopy would have to be discovered before progress could be made in this field.

While bronchoscopy undoubtedly was the best single procedure for diagnosing lesions in the larger bronchi or their immediate subdivisions, it was of little value in recognizing the more peripheral neoplasms. Reports from many large clinics showed that positive findings from bronchoscopic biopsies varied from 62 to 89 per cent of cases (1). The general experience, however, indicated that a large proportion of these tumors involved the larger bronchi and therefore were not amenable to surgical removal. It appeared that the percentage of positive diagnoses through bronchoscopic biopsies bore a definite direct ratio to the percentage of inoperable cases. In a majority of the series of cases reported, few authors showed a rate of successfully operated cases higher than 10 per cent. In a recent report, Norris (2) indicated that, of 269 cases of proved bronchogenic carcinoma, only 30 (12.9 per cent) were found suitable for resection.

The excellent results secured by Papanicolaou in the diagnosis of uterine carcinoma by vaginal smears and the sporadic finding of cancer cells in sputum of patients who had bronchogenic carcinoma suggested that the method of cytologic diagnosis by studying bronchial secretions should be investigated. Although sputum had previously been studied by us and by others in a certain number of cases, it was our experience that the number of positive diagnoses was insufficient to adequately supplement the inadequacy of the then existing diagnostic procedures. Since virtually all of our cases of suspected carcinoma were examined bronchoscopically, it was decided to utilize bronchoscopically removed secretions. We had previously been impressed by the finding of tubercle bacilli in bronchoscopically removed secretions in many cases when repeated studies of sputum were negative. In early carcinoma, sputum is either scant or absent and becomes profuse only when lesions become obstructive by interfering with

[1] From the Department of Broncho-Esophagology, Jefferson Hospital, Philadelphia, Pa.

[2] Presented before the Medical Section, as part of the symposium on *Laboratory and Research*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 4, 1949.

drainage. By bronchoscopy it was possible to obtain secretions in greater concentration from the lobar bronchi or from the segment suspected as the site of the tumor.

## TECHNIQUE

There were certain technical difficulties in the early cases but these have been overcome. In all suspected cases a routine bronchoscopy was carried out for diagnostic purposes in the customary manner. It is important that secretions be obtained from that portion of lung suspected as the site of cancer. Failure to recognize this has been responsible for a number of negative reports. In collecting secretions those in the trachea usually were discarded since they represented greater dilution, and secretions were obtained from the suspected bronchial subdivision. Because of their scantiness a special bronchoscopic collector was devised so that little dilution was required, even in these cases (figure 1). It is now routine practice to instill 3 to 5 cc. of isotonic sodium chloride solution

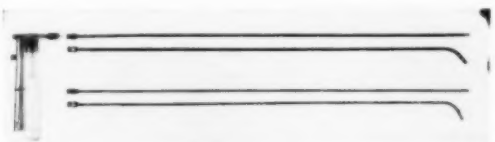

FIG. 1. Collector used to obtain secretions by bronchoscopy. The aspirating tips, either large or small, straight or curved, flexible-tipped, are interchangeable and are secured by a Luer lock.

bronchoscopically into the suspected subdivision. After several minutes the washings are aspirated into the collector and sent to the laboratory. Whenever possible, the patient is postured so that the solution is instilled into a dependant portion of the lung. If a right upper lobe bronchus is suspected as the site of carcinoma, the patient is placed on the right side after the bronchoscope is inserted, saline solution is then instilled, and the material aspirated. The patient is slowly returned to the dorsal position as the aspiration is continued. Utilization of this technique has definitely increased the number of positive diagnoses, particularly when the secretions are scant.

We have not found it satisfactory to make smears directly from bronchial secretions with the aid of a small gauze sponge carried through the bronchoscope. It is difficult to collect an adequate amount of secretion and the material dries so quickly that fixation is difficult.

There have been no changes in the technique of preparation of the smears or their staining. The method previously described still is rigidly followed (3).

As a result of this method of diagnosis to supplement the bronchoscopic findings either by direct vision and biopsy and the employment of telescopic inserts or the interpretation of anatomico-pathological changes as indicative of infiltrating neoplasm, it has been possible to diagnose cases of carcinoma which

are beyond the range of vision of the bronchologist and in which bronchoscopy is absolutely negative. These are the cases which previously offered a challenge diagnostically for, with negative bronchoscopic findings, the diagnosis could be made only by exploratory thoracotomy. Often these cases were not brought to a final conclusion diagnostically by surgical exploration until other diagnostic plans and therapeutic measures were tried and valuable time was lost.

## RESULTS

In a preliminary report made early in 1946, bronchoscopically obtained secretions stained by the Papanicolaou technique in a group of 30 consecutive cases of suspected carcinoma were diagnosed by cytologic examination as cancerous in 22 cases (73 per cent). In this same group a histologic diagnosis of carcinoma based on material from bronchoscopic biopsy was made in 11 cases (36 per cent) (4). In a paper presented at the meeting of the American Broncho-Esophagological Association later in 1946, studies of 57 proved cases of carcinoma were presented (1). A diagnosis of cancer by cytologic study of bronchoscopically removed secretions was made in 47 cases (82.4 per cent) and by bronchoscopic biopsy in 24 cases (42.1 per cent). While the difference between the percentage rates of 82.4 per cent for the positive cytologic diagnosis and 42.1 per cent for positive bronchoscopic biopsy is impressive, of more importance is the group of 23 cases in whom bronchoscopic biopsy was negative but a positive diagnosis could be made from the stained secretions.

Completed statistical data as of February 1949 include a total of 285 cases of bronchogenic carcinoma which were proved by bronchoscopic biopsy, cytologic examination of bronchoscopically removed secretions, exploratory thoracotomy, examination of metastatic lymph nodes, or at post-mortem examination. These cases have been examined since 1945, when this study was started. Of this group 253 (88.8 per cent) were diagnosed by cytologic examination of bronchoscopically removed secretions. In 99 cases (34.7 per cent) positive findings on bronchoscopic biopsy were obtained and in 78 there was bronchoscopic evidence of deformity, fixity, rigidity, or stenosis suggesting new growth. If this latter group are included with the cases of positive bronchoscopic biopsy, the total number of bronchoscopic diagnoses would be 177 (62.1 per cent). This still gives one a percentage rate of 26.7 in which bronchoscopy was absolutely negative. The difference on the basis of an histologic diagnosis is 54 per cent.

## CRITERIA FOR CYTOLOGIC DIAGNOSIS

A false positive diagnosis was made on one occasion. The patient had a large pulmonary abscess and pneumonectomy was performed on the basis of apositive cytologic diagnosis. Histologic study of the surgical specimen revealed a complete absence of carcinoma. It is very probable that errors of this type will not again be made, in spite of the appearance of metaplasia in pulmonary abscess and in bronchiectasis, if one closely adheres to the criteria for diagnosis of neoplastic cells.

It has been learned that, although such cells are squamous, they are never-

theless regular in shape, size, and staining qualities as compared with cancer cells. Furthermore, in cases of squamous metaplasia the cells, not being neoplastic, are cohesive and therefore remain in clumps. In carcinoma, the cells are quite irregular. Being neoplastic they are also incohesive, so that whenever some appear in clumps others are invariably scattered singly throughout the smears.

Thus, with accumulation of experience and the exertion of reasonable care, overdiagnoses should be negligible or entirely nonexistent.

In a number of instances, several bronchoscopic examinations are performed before a positive diagnosis is obtained, but in a majority the diagnosis is made on the first specimen of secretion. Repeated bronchoscopies more often are carried out in the presence of a pulmonary lesion suspected as malignant but with negative cytologic findings.

TABLE 1

*Bronchoscopic and Cytologic Findings and Occurrence of Metastasis to Regional Lymph Nodes*

| | | |
|---|---|---|
| Bronchoscopy negative | Cytology negative | 7 cases with no metastasis |
| Bronchoscopy negative | Cytology positive | 18 cases with metastasis in 2 cases |
| Bronchoscopic biopsy positive | Cytology positive | 21 cases with metastasis in 11 cases |
| Bronchial deformity, etc. | Cytology negative | 5 cases with metastasis in 4 cases |
| Bronchial deformity, etc. | Cytology positive | 18 cases with metastasis in 8 cases |

## FINDINGS ON SURGICAL EXPLORATION

While it has not been possible to evaluate the effects of this method of diagnosis on surgical results based on five year nonrecurrences, there has been opportunity to observe the findings at operation. To ensure uniformity in the surgical evaluation of these cases, we have included only those examined and treated surgically by Dr. John H. Gibbon, Jr. (5). No opinion can be given regarding the percentage of resectable cases in the entire series, for many either were inoperable, refused operation, or consulted surgeons elsewhere and were lost. Of 117 cases operated on by Doctor Gibbon, 48 were found to be nonresectable upon exploration; in 69, resection was performed. In 25 of the 69, there was gross evidence of metastasis to regional lymph nodes but resection of these was considered possible. The bronchoscopic and cytologic findings and the occurrence of metastasis to regional lymph nodes are shown in table 1.

In this group, therefore, with bronchoscopy negative in 25 cases and cytology positive in 18, two exhibited metastasis to regional lymph nodes. In the group either positive by bronchoscopic biopsy or on the basis of deformity, totalling 44 cases with 39 showing a positive cytology, slightly more than 50 per cent had metastasis to regional nodes.

## CYTOLOGIC STUDY OF SPUTUM

An increasing number of reports are appearing in the literature on the diagnosis of bronchogenic carcinoma by cytologic study of sputum. Outstanding among these are the writings of Woolner and McDonald (6), Watson and his associates

(7), Papanicolaou and Cromwell (8), Farber and his collaborators (9), and Freemont-Smith and his co-workers (10). Many of these reports exhibit a high percentage of positive findings which compare favorably with the results obtained by bronchoscopic study of secretions. It is of interest to recall that in 1945, when we first embarked on this study, only isolated case reports of carcinoma diagnosed by the cytologic study of sputum were reported in this country. Our findings, too, were not encouraging in spite of several excellent reports from Europe and England. The method of sputum study now appears to give good results and possesses certain advantages. It should be pursued further.


## SUMMARY

1. The cytologic diagnosis of bronchogenic carcinoma offers a means of recognizing early and peripherally situated lesions which cannot be visualized bronchoscopically or diagnosed accurately by any means short of actual biopsy of the tumor itself at exploratory thoracotomy.

2. The method requires special training in staining techniques and in the identification of the normal and abnormal cellular content of the tracheobronchial tree. This is not a remarkable situation in any histopathological problem.

3. False positive diagnoses cannot be prevented, but the incidence is low in the experience of the trained cytologist.

4. With earlier discovery of suspicious pulmonary lesions by mass roentgenographic surveys or similar techniques and by cytologic study of bronchial secretions, the end results of surgical treatment of bronchogenic carcinoma should exhibit marked improvement.



## CONCLUSIONES

### *El Valor del Diagnóstico Citológico de la Malignidad Pulmonar*

1. El citodiagnóstico del carcinoma broncógeno ofrece un medio de reconocer las lesiones tempranas y periféricas que no pueden visualizarse broncoscópicamente o diagnosticarse con exactitud por ningún medio aparte de la biopsia del tumor mismo en una toracotomía exploradora.

2. El método exige adiestramiento especial en las técnicas de coloración y en la identificación del contenido normal y anormal de las células del árbol tráqueobronquial, situación esta que no tiene nada de extraña en ningún problema histopatológico.

3. Aunque no pueden impedirse las seudopositivas, la incidencia de las mismas es baja en la práctica de un citólogo adiestrado.

4. Con el descubrimiento más temprano de las lesiones pulmonares sospechosas por medio de las encuestas radiográficas colectivas o de técnicas semejantes y por el estudio citológico de las secreciones bronquiales, los resultados terminales del tratamiento quirúrgico del carcinoma broncógeno deben mostrar decidida mejora.

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# PROPERTIES OF A CULTURE OF BCG GROWN IN LIQUID MEDIA CONTAINING TWEEN 80 AND THE FILTRATE OF HEATED SERUM[1]

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## INTRODUCTION

For reasons which have been discussed recently in this journal (8), it is probable that many of the irregularities observed in the response of experimental animals and man to the injection of the BCG vaccine stem from the fact that the batches of vaccine used for immunization differ greatly in physiological activity and antigenicity. The present paper describes the first of a series of experimental studies aimed at the development of a vaccine possessing better defined biological characteristics.

As shown elsewhere, one can obtain by the use of the Tween-albumin media young cultures of tubercle bacilli which are sufficiently well dispersed and homogeneous to allow their manipulation by the ordinary bacteriological techniques (4, 5, 6, 7, 9, 11, 12, 14). The dispersed character of the growth resulting from the wetting effect of Tween obviates in particular the necessity of resorting to prior grinding for the preparation of the bacterial suspension. Whereas the clumps of tubercle bacilli harvested from the conventional media contain only a small percentage of viable organisms (18), the "dispersed" cultures obtained in Tween-albumin solutions consist predominantly of living and physiologically active cells. This is demonstrated by the results of quantitative determinations of the numbers of colonies developing on oleic acid-albumin agar (14), and by the high degree of metabolic activity of the bacilli separated from the dispersed cultures (17). Likewise of importance is the fact that a number of standard cultures of mycobacteria which have been maintained for some three years in this laboratory by weekly passage in Tween-albumin media have retained unaltered their morphological and biological properties, and in particular their characteristic level of virulence. Thus, whereas the human strains H37Rv[2] and Jamaica #22[2], and the bovine strains Ravenel[2] and Vallée[2] have remained pathogenic for guinea pigs and mice, the avirulent variants of human strains H37Ra[2], JH16Ra[2], and H4Ra[2] are still completely avirulent for these animal species. Similarly, the attenuated human strain R1Rv[2] and three different strains of BCG have also remained constant in their property of giving rise to discrete pulmonary lesions in mice (following intravenous injection) without being capable of causing progressive disease in normal mice, guinea pigs, or rabbits. Further evidence of the stability of cultures in Tween-albumin media is found in the fact that all cultures

[1] From the Rockefeller Institute for Medical Research, New York, N. Y.

[2] These strains were originally obtained through the generous cooperation of Dr. Jules Freund (Ravenel and Jamaica strains), Mr. William Steenken (H37Rv, H37Ra, JH16Ra, H4Ra, and R1Rv strains) and Dr. Hubert Bloch (Vallée strain).

mentioned above have maintained their characteristic colonial morphology on oleic acid-albumin agar, the serpentine pattern of growth ("cord formation") which they exhibit remaining unchanged and in direct relation to the level of virulence (7, 15).

It occurred to the writers that these properties of the Tween-albumin media might permit the preparation of cultures of BCG possessing constant and predictable physiological and antigenic characteristics. The findings to be outlined in the present paper describe from this point of view the activity *in vitro* and *in vivo* of a strain of BCG cultivated in a medium in which the filtrate of human serum heated at acid reaction served as a source of albumin.

## EXPERIMENTAL

*Basal culture medium:* The basal medium used was essentially that described in earlier studies for the growth of mycobacteria under submerged conditions (9, 11). As the three BCG cultures so far tested respond particularly well to the dispersing effect of Tween 80, a final concentration of 0.02 per cent of this agent in the medium has been found sufficient to yield stable, dispersed growth. Addition of glucose or glycerin to the basal medium increases the yield of bacterial cells but may under certain conditions decrease their viability (10). Consequently, these additional sources of energy have been omitted from the medium, as viability was deemed more important than the yield of bacterial cells in experiments aiming at the establishment of immunity.

The medium was prepared as follows:

| | | |
|---|---|---|
| $KH_2PO_4$ | 1.0 Gm. | |
| $Na_2HPO_4 \cdot 12H_2O$ | 6.3 Gm. | |
| Asparagin | 2.0 Gm. | |
| Tween 80 | 0.2 Gm. | |
| Enzymatic digest of casein | 0.5 Gm. | |
| Distilled water | 900 cc. | |
| Add: | | |
| Ferric ammonium citrate | 0.05 Gm. | |
| $MgSO_4 \cdot 7H_2O$ | 0.01 Gm. | (1 cc. of a 1 per cent stock solution in distilled water) |
| $CaCl_2$ | 0.0005 Gm. | (1 cc. of a 0.05 per cent stock solution in distilled water) |
| $ZnSO_4$ | 0.0001 Gm. | (1 cc. of a 0.01 per cent stock solution in distilled water) |
| $CuSO_4$ | 0.0001 Gm. | (1 cc. of a 0.01 per cent stock solution in distilled water) |

Adjust pH to 6.5-6.8

The medium was distributed in 25 cc. amounts in Erlenmeyer flasks of 250 cc. capacity and was autoclaved at 15 lbs. pressure for 15 minutes.

*The use of filtrate of serum heated at acid reaction as source of albumin:* It has been previously shown that the albumin fraction of serum (Plasma Fraction V of the alcohol fractionation method developed by Cohn, *et al.*) exerts on tubercle bacilli a growth-enhancing effect which depends upon two independent mechanisms: (a) Fraction V protects the bacilli against a variety of toxic influences; and (b) supplies them with some accessory growth factor, as yet unidentified (4,

6, 7, 9, 11). In the past, the Fraction V of bovine plasma[3] has been used almost exclusively as a source of albumin. Unfortunately, this material is costly and not readily available to workers outside the United States. Moreover, as BCG cultures may be used for vaccination of human beings, it appears undesirable to add protein of animal origin which might act as antigen to the culture media in which the bacteria are grown. Consequently, an attempt has been made to find an inexpensive and convenient method for the separation from human serum of a fraction which would have the same growth-promoting properties as the Fraction V separated from plasma by the Cohn method.

The technique which has given the best results in this laboratory is based on the fact that, at acidic reactions, serum albumin can be heated to high temperatures without undergoing denaturation and without losing the associated properties responsible for the enhancement of growth of tubercle bacilli. The serum globulins, on the contrary, become completely denatured under the same conditions. The technique is carried out as follows:

Serum is acidified to pH 2.0 to 2.5 by the addition of normal HCl (approximately 0.5 to 0.8 cc. of normal acid per 10 cc. of serum). It is then heated at 65° to 70°C. for 20 minutes. The heated serum, which should remain fluid and transparent, is cooled and brought back to pH 6.5 by the careful addition of 0.1N sodium hydroxide. An abundant precipitate separates, which consists chiefly of denatured globulins, while a large part of the albumin remains in solution. The denatured insoluble proteins are then removed by filtration through filter paper or by centrifugation. In some instances, however (and particularly in the case of human sera), the precipitate is of such a fine colloidal nature as to prevent separation. Under these circumstances, separation may be effected by the addition of a small amount (approximately one-tenth the volume) of a water-immiscible organic solvent (chloroform or ether, for example) to the heated serum which has been brought back to pH 5.0. Gentle agitation causes immediate agglutination of the precipitate which then can be readily separated from the soluble part by filtration.

Sterilization of the filtrate can be carried out by a second filtration through bacteriological porcelain candles. In this laboratory the candles are first cleaned with water, then baked in an electric oven at 500°C., and washed again with water prior to sterilization. Although it is possible and convenient to sterilize albumin solutions by filtration through asbestos pads of the Seitz type, care must be taken that the pads are thoroughly washed before use as they often release impurities which interfere with the growth of tubercle bacilli. It is advisable to heat the sterilized filtrate up to 55°C. for 20 minutes in order to distill off the traces of organic solvent left after removal of the precipitate of denatured proteins.

The concentration of albumin in the filtrate of heated serum can be determined by precipitation with 5 per cent trichloracetic acid or 2.5 per cent sulfosalicylic acid. In our experience, approximately 60 per cent of the original albumin in the serum is recovered in the filtrate by the technique outlined above, whether the filtrate be prepared from the serum of man, ox, horse, or rabbit.

In the present experiments, the filtrate of heated human serum was added aseptically to the autoclaved basal medium in amounts of 5 cc. (of filtrate at pH 6.5) for 25 cc. of medium.[4]

[3] Produced commercially by the Armour Laboratories, Chicago, Illinois.

[4] Many of the experiments described in the present report were carried out with samples of filtrates of human heated serum received through the generous cooperation of Mr. C. E. Bender of Microbiological Associates, Flemington, New Jersey.

*The BCG Culture*

Although the three different strains of BCG available in our laboratory have been cultivated successfully in the medium described above, all experiments to be reported here have been carried out with one single strain (Phipps). It was received through the courtesy of Dr. Joseph Aronson and is used for the preparation of BCG vaccine at the Henry Phipps Institute.

Flasks containing approximately 30 cc. of the medium prepared with Tween and serum filtrate were inoculated by adding 3 cc. of the BCG culture grown for eight days at 37° C. in the same medium. After one week of incubation, the new growth was very abundant and well dispersed. It was seen on the bottom of the flask as a fine sediment which could readily be resuspended by gentle manual shaking to give a macroscopically homogeneous suspension. Microscopic examination revealed the presence of clumps of various dimensions (some containing probably up to one thousand bacilli) in addition to many smaller clumps and isolated bacterial cells. The bacilli took the acid-fast stain but the cells were somewhat shorter than those present in a sample of vaccine prepared from the same strains by the conventional technique at the Henry Phipps Institute (1a).

*Colonial morphology:* In order to study the colonial morphology of the cultures growing in Tween-serum filtrate medium, dilutions of these cultures in 0.1 per cent albumin in saline were spread on the surface of oleic acid-albumin agar in Petri dishes, the albumin used for the dilutions and the preparation of the agar medium being Armour's bovine plasma Fraction V (11, 14). Colonies of uniform morphology developed, which exhibited some tendency to spread over the surface of the agar medium. The serpentine pattern of growth was less pronounced than in the case of the fully virulent cultures but was nevertheless obvious enough to allow a ready distinction between the BCG colonies and the raised opaque colonies of the fully avirulent variants (15). The comparative colonial morphology of the three culture types is illustrated in figure 1.

*Virulence for animals:* The culture of BCG grown in liquid medium containing Tween and the filtrate of heated serum retained its characteristic degree of attenuation for experimental animals. Albino mice, five weeks old, weighing approximately 20 Gm., were injected into the tail vein with 0.2 cc. of undiluted culture. The animals remained in apparent good health and continued to gain weight, although many discrete, nonprogressive pulmonary lesions were seen when they were sacrificed two months later. Guinea pigs inoculated intramuscularly with 0.1 cc. of the same undiluted culture also continued to gain weight and failed to reveal macroscopic tuberculous lesions when sacrificed after three months. These results become the more significant in view of the fact that the cultures used for the virulence tests contained many more living bacilli (from one hundred to ten thousand times more per unit volume) than the bacterial suspensions used as vaccines in the conventional procedures. No information is available concerning the response of human beings to cultures of BCG grown in media containing Tween and the filtrate of heated human serum.

*Viability of the Cultures*

It had been found in earlier studies from this laboratory that well-dispersed cultures of tubercle bacilli in Tween-bovine albumin medium were capable of initiating growth regularly with inocula of $10^{-8}$ cc. and occasionally with $10^{-9}$ cc.,

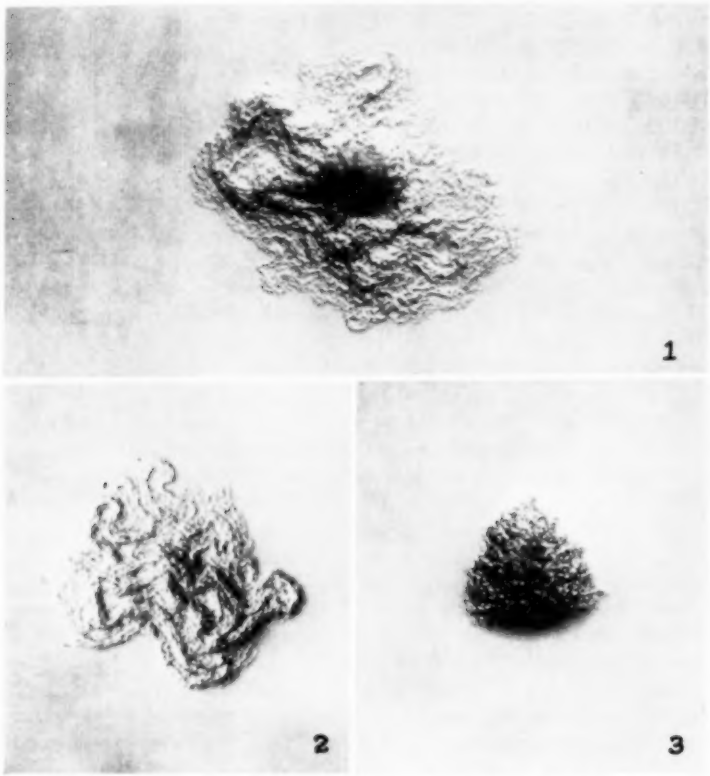


FIG. 1. Comparative colonial morphology of three strains of tubercle bacilli:
(1) BCG (strain obtained from the Henry Phipps Institute)
(2) H37Rv (virulent human strain)
(3) H37Ra (avirulent variant of H37Rv)
All colonies are from a 9-day growth on oleic acid-bovine albumin agar. × 230.

a finding which suggested that most of the cells in the cultures were viable (4, 9). This conclusion has received much support from more recent investigations based on the statistical analysis of the number of colonies developing on the surface of oleic acid-albumin agar plates inoculated with proper dilutions of cultures in liquid Tween-bovine albumin medium (14). Similar studies carried out with cultures of BCG, cultivated in media containing the filtrate of heated human serum

in lieu of bovine albumin, have yielded similar results and have led to the following conclusions:

Cultures of BCG grown as described earlier in this report reach in eight days a density and a bacterial population corresponding to approximately three-fourths of the maximal population of viable bacteria to be obtained on further incubation. The maximum level is reached after two to three weeks of incubation.

Addition to the medium of 0.1 per cent glucose approximately doubles the final density of the culture and the bacterial population (as measured by the number of colonies growing on oleic acid-albumin agar). Still higher bacterial counts are obtained during the first week of incubation if the amount of sugar is increased up to 0.5 per cent. With this higher sugar content, however, there soon occurs on further incubation a sharp fall in the number of viable cells although the turbidity of the culture does not decrease at the same time. Microscopic study reveals that many of the bacilli are then undergoing morpholog-

TABLE 1

*Viability of BCG (Phipps) Culture in Liquid Medium Containing Tween and the Filtrate of Heated Human Serum*

| PREPARATION | INCUBATION 37°C. | STORAGE (ICEBOX) | COLONIAL COUNT* (PER CC. OF CULTURE) |
|---|---|---|---|
| I | 8 days | 0 | $20 \times 10^6$ |
| II | 8 days | 0 | $50 \times 10^6$ |
| II | 8 days | 3 weeks | $19 \times 10^6$ |
| III | 8 days | 0 | $61 \times 10^6$ |
| III | 8 days | 6 weeks | $54 \times 10^6$ |

* Average of counts made on 5 plates of oleic acid-albumin agar. Colonial counts do not describe exactly the number of viable cells as the bacterial suspensions contain many microscopic clumps in addition to single cells.

ical alteration and are losing the acid-fast property. Similar or even more pronounced loss of viability has been observed when glycerin was substituted for glucose in these experiments (10).

Cultures (without glucose) incubated for eight days at 37° C., and then placed in the refrigerator at 4° to 7° C. for periods of three or six weeks, do not exhibit any detectable alteration in cellular morphology or any decrease in viability during storage. Longer periods of refrigeration were not tested.

Some of the findings concerning the effect of storage on viability are recorded in table 1. It must be kept in mind that the number of living cells present in the cultures is considerably larger than would appear from the number of colonies, as the cultures in Tween-serum filtrate medium contain many microscopic clumps in addition to isolated organisms.

### *Response of Guinea Pigs to the Injection of BCG Cultures Grown in Media Containing Tween and the Filtrate of Heated Human Serum*

Although cultures of BCG grown in Tween-serum filtrate medium appear unable to cause progressive disease, it is likely that they can multiply to some ex-

tent in the body of normal guinea pigs. This fact is strongly suggested by the results presented in table 2, where it is shown that injection of very small amounts of culture (0.000001 cc.), containing but a few infective units, was sufficient to sensitize guinea pigs to tuberculin.

It will be noted that sensitization was also established following the injection of 0.1 cc. of cultures kept for three or six weeks in the refrigerator. The desirable quantitative data are not yet available to establish whether, during refrigeration, sensitizing ability had been retained to the same degree as viability.

TABLE 2

*Sensitization of Guinea Pigs with Fresh and Old Cultures of BCG in Liquid Medium Containing Tween and the Filtrate of Heated Human Serum*

| BCG | | | PPD† | TUBERCULIN REACTION |
|---|---|---|---|---|
| Preparation* | Storage (icebox) | Amount injected | | |
| | | *cc.* | *mg.* | |
| I | 0 | 0.1 | 0.0005 | ++++ |
| I | 0 | $0.1 \times 10^{-5}$ | 0.0005 | ++ |
| I | 0 | $0.1 \times 10^{-6}$ | 0.0005 | 0 |
| II | 3 weeks | 0.1 | 0.0005 | ++++ |
| III | 6 weeks | 0.1 | 0.0005 | ++++ |
| Medium | 0 | 0.1 | 0.005 | 0 |

* Incubated at 37°C. for 8 days (see table 1).

† PPD (0.1 cc. of solution in saline) injected intracutaneously 6 weeks after vaccination with BCG culture. Readings made 24 and 48 hours later.

An experiment was instituted to test the effect of vaccination with BCG on the resistance of guinea pigs to the subcutaneous injection of virulent human bacilli. The animals, divided into 7 groups, were treated as indicated on page 73.

A detailed account of the fate of the individual animals in the seven different groups is now in course of preparation and will be published elsewhere (13). Only a brief summary of the general trend of the results will be presented here.

All animals which had received the BCG culture alone (groups IB and IIB) continued to gain weight at a normal rate, and did not reveal any macroscopic tuberculous lesions on examination post mortem.

All animals infected with the virulent human strain without prior vaccination (group V) began to lose weight within two weeks after infection and reached an extreme degree of emaciation. Ten had already succumbed when the experiment was terminated nine weeks after infection, and all survivors were found to have generalized tuberculosis of such an extent that they probably would have died soon thereafter.

The animals of the four other groups (which received both the BCG culture and the challenge infection) exhibited a fairly uniform pattern of response. Most of them continued to gain in weight after the challenge infection, although some-

what more slowly than the control animals. Only a few (approximately 10 per cent) exhibited signs of emaciation and only one died of tuberculosis. Post-mortem examination revealed macroscopic tuberculous lesions in all animals. In general the lesions were limited to a few tubercles in the spleen and liver, but in some cases they were widely distributed throughout the tissues. These were the same animals which showed severe emaciation. Thus, all four preparations

| EXPERIMENTAL GROUPS | NUMBER OF GUINEA PIGS | BCG VACCINATION | CHALLENGE INFECTION (SUBCUTANEOUS ROUTE) 7 WEEKS AFTER VACCINATION |
|---|---|---|---|
| IA | 16 | 0.1 cc. of vaccine prepared at the Henry Phipps Institute.† | 0.1 cc.‡ |
| IB | 8 | 0.1 cc. of vaccine prepared at the Henry Phipps Institute.† | 0 |
| IIA | 17 | 0.1 cc. of fresh culture in Tween-human serum filtrate medium.* | 0.1 cc.‡ |
| IIB | 8 | 0.1 cc. of fresh culture in Tween-human serum filtrate medium.* | 0 |
| III | 17 | 0.1 cc. of culture in Tween-human serum filtrate medium* stored for 3 weeks in ice-box. | 0.1 cc.‡ |
| IV | 17 | 0.1 cc. of culture in Tween-human serum filtrate medium* stored for 6 weeks in ice-box. | 0.1 cc.‡ |
| V | 16 | 0 | 0.1 cc.‡ |

* All these cultures were incubated at 37 °C. for 8 days.

† This BCG vaccine, prepared according to the classical technique (1a), was shipped from Dr. Aronson's laboratory immediately upon completion, and injected the next day into the experimental guinea pigs at The Rockefeller Institute.

‡ Undiluted culture of human strain of tubercle bacillus (Amerzanga) incubated for 8 days in Tween-bovine albumin medium. This culture was kindly sent us by Dr. Aronson.

of vaccine elicited a demonstrable degree of protection against infection by the subcutaneous route, but the results did not reveal any convincing difference between them. It is possible, however, and indeed is considered likely, that differences could have been brought out by changing the design of the experiment in regard to such factors as: the amount of vaccine used, the size of the challenge dose, the time elapsed between vaccination and challenge, and the route of infection.

## DISCUSSION

The results of the experiments which have just been outlined seem to show that the BCG culture, which had grown diffusely and rapidly below the surface of the medium containing Tween and the filtrate of heated human serum, had retained its characteristic biological properties. It failed to establish progressive disease in mice and guinea pigs; it was capable of converting guinea pigs to the tuberculin-positive state; and it increased their resistance to artificial infection (by the subcutaneous route) with virulent human tubercle bacilli.

Needless to say, the present data do not establish that BCG vaccination brought about a true state of immunity, for the introduction of the challenge-infecting dose by the subcutaneous route did not allow adequate differentiation between the effect of allergy and immunity (8). The results demonstrate only that the culture grown in the Tween-serum filtrate media compared well qualitatively with the vaccines prepared by the conventional technique (1a, 1b) and may even present definite advantages over the latter from the quantitative point of view. The content of viable, physiologically active cells in the culture is extremely high, as shown by colony counts and by the ability of very minute amounts of culture to elicit the tuberculin-positive state in guinea pigs. Moreover, the number of viable cells is predictable and remarkably stable even after prolonged periods of incubation or of storage. This stability should greatly facilitate the planning of immunity experiments and the analysis of their results.

Other minor advantages of the dispersed cultures deserve brief mention, namely: the rapidity with which they can be obtained; the fact that they require for their preparation only standard bacteriological techniques; the elimination of the transfer operations and of the necessity of grinding the bacterial growth before distribution of the final product; and their stability in the very medium in which they are grown which allows ample time for the performance of the control tests required of all biological products. Nevertheless, it is obvious that the technique of cultivation of BCG outlined in the present report should be regarded only as an experimental procedure and not as one recommended for the preparation of the vaccine. It constitutes, however, a demonstration that one can obtain by adequate cultural methods bacterial suspensions of dependable physiological and antigenic activity.

## SUMMARY

A simple technique is described for the preparation from human and animal sera heated at acid reactions of a filtrate which can replace the albumin fraction for the cultivation of tubercle bacilli.

Cultures of BCG grow rapidly and diffusely in a liquid medium containing this crude albumin fraction of human serum and a small amount of the wetting agent Tween 80.

The cultures obtained under these conditions consist predominantly of cells which are viable and physiologically active. Quantitative colonial counts reveal that the bacilli retain their viability for prolonged periods of time under ordinary conditions of refrigeration and even at 37° C.

Cultures of BCG grown diffusely in media containing Tween 80 and the filtrate of heated human serum retain unaltered their characteristic degree of attenuated virulence and their ability to elicit in guinea pigs both tuberculin allergy and an increased resistance to subcutaneous infection with virulent human tubercle bacilli.

It is possible to sensitize guinea pigs with very minute amounts of dispersed culture (0.000001 cc.) containing only a few viable units. The homogeneity and stability of the cultures, even after prolonged periods of storage, greatly facilitate

the operations required for the preparation, distribution, and biological control of the vaccine.

SUMARIO

*Propiedades de un Cultivo de BCG Sembrado en Medios Líquidos que Contenían Tween 80 y el Filtrado de Suero Calentado*

La sencilla técnica descrita es para la preparación, de sueros humanos y animales calentados a reacciones ácidas, de un filtrado que suplante la fracción de albúmina en el cultivo de bacilos tuberculosos.

Los cultivos de BCG crecen rápida y difusamente en un medio líquido que contenga la fracción de albúmina bruta del suero humano y una pequeña cantidad del humectante Tween 80.

Los cultivos obtenidos en esas condiciones constan predominantemente de células viables y fisiológicamente activas. Las numeraciones cuantitativas de las colonias revelan que los bacilos retienen su viabilidad por períodos prolongados de tiempo en las condiciones ordinarias de refrigeración y hasta a 37°C.

Los cultivos de BCG sembrados difusamente en medios que contienen Tween 80 y el filtrado de suero humano calentado retienen, sin alteración, su característica virulencia atenuada y su capacidad para evocar en los cobayos tanto alergia a la tuberculina como mayor resistencia a la infección intramuscular por bacilos tuberculosos humanos virulentos.

Resulta posible sensibilizar a los cobayos con cantidades pequeñísimas (0.000001 cc.) de cultivo disperso, que sólo contengan algunas unidades viables. La homogeneidad y estabilidad de los cultivos, aun después de prolongados períodos de conservación, facilitan considerablemente las operaciones requeridas para la preparación, distribución y control biológico de la vacuna.

*Acknowledgment*

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# EXPERIMENTAL TUBERCULOSIS IN THE DOG[1,2]

## Comparison of Lesions in Puppies and in Mature Dogs

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### INTRODUCTION

The rate of development and form of lesions in pulmonary tuberculosis of human beings are so varied and unpredictable that little accurate information has become available with regard to the relative importance of factors in the host which tend to favor or resist the spread of tuberculous infections. Factors related to the infective bacteria must necessarily be appraised on the basis of results in animal experiments in which the size of the infecting dose can be accurately measured. Dosage is an unknown and highly variable factor in the human disease and, perhaps for this reason, is usually ignored in the clinical literature in spite of the facts which have shown its critical importance in experimental tuberculosis. Similarly, any serious consideration of the virulence of various strains of tubercle bacilli which are involved in the different forms of pulmonary tuberculosis in man has been largely neglected except that "bovine" strains and "human" strains have been separated by tests in rabbits. Even in these tests, all too often the dosage is not measured with sufficient accuracy.

Of the factors which are related to the host, inherited susceptibility is thought to be important in human tuberculosis as it has been proved to be in some species of animals used for experimentation, but its relative importance cannot be known so long as other factors are neither measurable nor controllable. The factors of age and sex appear to have considerable importance, but it is not yet known just how much their influence is dependent upon their association with factors in external environment and therefore related to frequency of exposure to infection and to diet, rest, work habits, and many other variable influences. The greater susceptibility of females past the age of puberty as compared with that of males of the same age has not been conclusively substantiated by controlled animal experiments. There is some experimental evidence that young guinea pigs are more resistant than older ones (1) and that there is a progressive decline of resistance to tuberculosis with advancing age.

The once accepted theory that childhood tuberculosis is in some fundamental way different from tuberculosis in adults has been supplanted by the theory that the observed differences are due to the presence or absence of acquired immunity and hypersensitivity. Therefore, instead of referring to "childhood

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[2] The animal experiments which form the basis of this paper were carried out in the Department of Pathology, Northwestern University Medical School, and the work was assisted by a grant from the Committee in Scientific Research of the American Medical Association.

tuberculosis" and "adulthood tuberculosis" the trend of teaching in this country has led to the practice of classifying the disease as "primary tuberculosis" and "postprimary" or "reinfection tuberculosis." Serious disagreement persists with regard to the interval of time following first infection after which a "primary infection" becomes a "secondary" or "reinfection type." Up to the time of the refinement, standardization, and routine use of the intradermal (Mantoux) tuberculin test, there was no reliable means of determining the time of infection in human cases. At present the time of first infection is determined with a satisfactory degree of accuracy in some cases, particularly in institutions in which the test is used frequently and at regular intervals. Evidence is accumulating, however, to show that cutaneous hypersensitivity to tuberculin does not persist indefinitely after the complete healing of lesions. A complete record of tuberculin reactivity, beginning with early childhood, will be necessary to establish with certainty in any case the occurrence or absence of previous tuberculous infection. Morphological evidence obtained from roentgenography or from necropsy material cannot be interpreted intelligently unless positive information regarding the time of exposure and records of cutaneous sensitivity to tuberculin are available.

In the past, a certain type of arrested lesion in the lung was assumed to be the result of a first infection (primary tubercle) and this with residues in the drainage lymph nodes is even now designated as a "primary complex" (Ranke). An impressive accumulation of evidence has been published by Terplan (2) to show that such complexes may be multiple and of different ages in the same individual. Such evidence requires the assumption either that the allergy acquired during the evolution of the first tuberculous infection has died out or that allergy does not regularly modify the form and course of a lesion which results from reinfection. The results of experiments on pulmonary tuberculosis in dogs support the latter view (3). The evidence so far published from observations on human cases is insufficient to permit a final decision on this question. A very large number of cases must be studied with a view to establishing the role of hyper-reactivity to the poison of the tubercle bacillus in the modification of the tissue response to infection before we can speak of "reinfection type" as more than a convenient term for conveying a certain vague clinicopathologic concept. Such a concept has little support from animal experiments under controlled conditions. The idea that necrosis and cavitation in tuberculous lesions of the lung are manifestations of the Koch phenomenon in previously sensitized animals does not bear careful analysis. The fact that in human pulmonary tuberculosis a lesion may be present for months or years before it cavitates should be sufficient evidence to exclude such a conception from serious consideration. In experimental canine tuberculosis, cavitation is similarly timed and equally extensive in lesions resulting from first infections and infections in previously sensitized animals (3). There are differences in form of tuberculous lesions in dogs just as there are differences in form of clinical tuberculosis, but these differences apparently depend much more upon individual susceptibility and upon the size of the infecting dose than upon altered reactivity of the tissues as a result of

previous infection. This report is concerned principally with the influence of age upon the form and extent of tuberculous lesions.

## MATERIALS AND METHODS

The dogs which were the subjects of this analysis consisted of 30 which were injected as puppies, six weeks to eight months of age, and 53 older dogs, all of which were injected with various doses of tubercle bacilli by the intrabronchial route. Of the puppies, all except 9 were born in the animal quarters of the laboratory and, after weaning, were fed with fresh milk, cod liver oil, and a meat-bread-vegetable mixture similar to that used to feed the mature dogs. All were assumed to be of mixed breeds since they were the offspring of dogs obtained from the pound. Most of the puppies and most of the mature dogs were used as "primary" controls in experiments on BCG vaccination or in reinfection experiments. A few were used in orientation experiments for the purpose of determining in puppies the size of the lethal dose of tubercle bacilli when injected intrabronchially.

For purposes of comparison, the puppies were divided into two groups according to age at the time of injection, those which were one and one-half to three months old forming the first group and those five to eight months old the second group. Such a division has the disadvantage that the number of dogs in each group is too small for statistical comparison but has the advantage of permitting comparison of lesions in three different age groups.

In order to compare statistically the lesions resulting from single inoculations in the puppies with those resulting from similar inoculations in fully mature dogs, the protocols, tissues, and microscopic sections from 53 adults were selected in the following manner. From the entire available number of 68 older dogs which had been subjected to a single intrabronchial inoculation of virulent, human type (G2) (4) tubercle bacilli, 11, which had died from intercurrent bronchopneumonia or had been sacrificed earlier than eight days after inoculation, and 4, in which no certain evidence of a tuberculous infection could be found at necropsy, were eliminated. Most of the dogs had been obtained from the pound and their ages were entirely unknown. Two showed by their rapid growth that they were young dogs, perhaps under one year, at the time of injection. One (No. 128) almost doubled its weight (12 Kg. to 19.7 Kg.) after the time of injection. With these two exceptions, all of this group appeared to be fully mature and can be considered as more than one year old before the beginning of experimentation.

The strain of tubercle bacilli used for injecting all of the 30 puppies and 53 adults was a moderately virulent, human type strain (G2), grown on egg yolk-glycerin medium which has been used in this laboratory over a period of about nine years. All injections were made by intrabronchial insufflation through a bronchoscope and, with a few exceptions, measured quantities of four-weeks-old cultures were mixed with 3 to 5 per cent mucin for injection. Since the details of technique have been previously described (3, 4) they will be omitted from this paper.

## RESULTS

### *Deaths from Tuberculosis*

Since the doses are not in every case comparable in the three groups (two groups of puppies and one of adults), the comparative rates of mortality in the groups as a whole have little significance. For example, in a titration experiment with two-month-old puppies, 25.0 mg. doses were used in 3 of a group of 9, and in no case have doses of comparable size been used in animals of the other two groups. The maximal doses in all other experiments have been 10 mg. In the titration experiment on 9 two-month-old puppies, 3 were given intrabronchial inoculations of 25 mg. each (13.5 to 17.2 mg. per Kg.) of human type culture

in 0.5 cc. of 5 per cent mucin, 3 were inoculated similarly with 5.0 mg. doses, and 3 with 1.0 mg. doses. The 3 which received the largest doses died of tuberculosis in 57, 106, and 116 days, respectively. One of those which received a 5.0 mg. dose died of tuberculosis in 1,041 days; one died with symptoms of encephalitis in 86 days but showed at necropsy active tuberculous lesions in lungs and liver; and one was killed with ether 108 days after inoculation. In the 3 which had received 1.0 mg. doses, there was one death after 90 days, probably from tuberculosis, and one after 86 days which could not be satisfactorily explained on the basis of the small, sharply limited, pulmonary lesions which were the only lesions found at necropsy. Both of these puppies exhibited "encephalitic fits" for several days before death but microscopic sections failed to show any definite evidence of an inflammatory process in the brain. The third dog of this group was killed with ether after 1,093 days.

In the younger group of 18 puppies, there were 12 which received doses of 2.0 mg. or less, and only one of these died of tuberculosis. Three died of acute pneumonia 11, 15, and 18 days after injection and the rest were sacrificed after various intervals from 8 to 1,233 days.

In the group of 12 older puppies, inoculated at ages of five to eight months, there were 7 which were subjected to intrabronchial insufflation with doses of 3.0 to 7.0 mg. Two were killed with ether after 19 days, one died of nontuberculous disease after 44 days, and 3 of the remaining 4 died of tuberculosis after periods of 25, 29, and 36 days. Each of the remaining 5 puppies of this group received doses of 0.26 to 0.5 mg. and in only one of these was death attributable to tuberculosis. In this dog, dead on the five hundred and fortieth day, death was due to rupture of the abdominal aorta at the site of a tuberculous lesion in the para-aortic lymph nodes.

These results are similar to those previously observed after injection of fully mature dogs with similar doses of tubercle bacilli.

When the mortality rate was computed on the basis of milligrams of tubercle bacilli per kilogram of dog's weight, essentially the same results were obtained but, with this method also, the doses were not strictly comparable. In a comparison of the figures in each group as a whole without regard to dose, the group of younger puppies showed a death rate from tuberculosis of about 50 per cent as compared with 44 per cent in the group of older puppies and 41 per cent in the mature dogs (table 1). When the figures for the two groups of puppies were combined and broken down according to size of dose per kilogram, the puppies showed a rate of 20 per cent in those receiving 0.1 mg. of tubercle bacilli per kilogram (dosage Group A in table 1) as compared with about 29 per cent in the mature dogs which received doses of 0.053 to 0.149 mg. per Kg. Moreover, in the larger number of puppies which received 0.427 to 1.25 mg. per Kg., the rate was 40 per cent, while in the mature dogs receiving 0.25 to 1.06 mg. per Kg. the rate was 45 per cent. The other figures for dosage in the puppies were in a much higher range (3.23 to 17.23 mg. per Kg.) with a death rate of 83.3 per cent, and were not comparable with any similar dosage in the mature dogs. In every case of computation of death rate from tuberculosis, those dogs which were

sacrificed within 100 days after injection or died of acute nontuberculous infections were excluded from the calculation. All that can be claimed for these figures, which are based upon relatively small numbers of dogs in each group, is that they do not indicate any pronounced difference in degree of susceptibility to tuberculosis among the animals of different age groups which received approximately the same doses of tubercle bacilli.

TABLE 1

*Size of Dose and Death Rate from Tuberculosis*

| | DOSAGE GROUP A 0.053 TO 0.149 MG. PER KG. | DOSAGE GROUP B 0.25 TO 1.25 MG. PER KG. | DOSAGE GROUP C 3.23 TO 17.23 MG. PER KG. | ALL DOSES 0.053 TO 17.23 MG. PER KG. |
|---|---|---|---|---|
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Puppies, Group 1, 1½ to 3 months (18) | | 16.7 | 83.3 | 50 |
| Puppies, Group 2, 5 to 8 months (12) | 20 | 75 | | 44.4 |
| All puppies (30) | 20 | 40 | 83.3 (only Group 1 represented) | 47.6 |
| Adult Dogs (53) | 28.6 | 45 | | 40.7 |

TABLE 2

*Incidence and Form of Lesions in Lungs and Lymph Nodes*

| | 15 PUPPIES 1½ TO 3 MONTHS | 12 PUPPIES 5 TO 8 MONTHS | 53 ADULTS |
|---|---|---|---|
| | *per cent* | *per cent* | *per cent* |
| Caseation, primary focus | 6 (40) | 2 (16.6) | 17 (32.1) |
| Calcification, primary focus | 10 (66.6) | 3 (25) | 2 (3.8) |
| Cavity formation | 3 (20) | 2 (16.6) | 20 (37.7) |
| Hypertrophy, lymph nodes | 9 (60) | 11 (91.7) | 34 (66.6) |
| Hyperplasia,* lymph nodes | 11 (73.3) | 9 (75) | 38 (71.7) |
| Caseation, lymph nodes | 6 (40) | 4 (33.3) | 14 (26.4) |
| Calcification, lymph nodes | 6 (40) | 3 (25) | 1 (1.9) |
| Hematogenous lesions | 4 (26.6) | 6 (50) | 28 (58.3)† |

* This refers to epithelioid transformation of macrophagic cells.

† Complete microscopic sections studied in a total of 48 dogs of this group.

### *General Form of Primary Lesions*

Since the proportion of cases of progressive and fatal tuberculosis in relation to the total number of dogs used was roughly the same in each group, it was concluded that nothing was gained in accuracy or clarity by eliminating any of the dogs from the comparison of types of lesions in the lungs, lymph nodes, and abdominal viscera, except the 3 puppies which received 25 mg. doses. The following comparisons include the complete list of dogs, except these 3, regardless of dosage and outcome (table 2). It will be seen, however, that dosage in an important degree determines the extent of caseation and cavitation in the primary lesions. An attempt will be made in the discussion of results to make adjustments for differences in dosage.

In a preliminary survey of the material to ascertain whether or not there were outstanding differences in size or composition of the primary pulmonary lesions in the different age groups, the data for the puppies in the younger age group were tabulated and compared with data from the older puppies and with those from the mature dogs. The comparisons were made between lesions of comparable age resulting from injections of similar doses of tubercle bacilli. A comparison of the products of the three principal diameters of the primary lesions showed no consistent differences. The more massive lesions occurred sometimes in the puppies and sometimes among the mature dogs, in spite of the fact that a larger proportion of the older puppies received doses in the higher ranges. Similarly, the form of the lesions showed no significant differences when lesions of comparable ages were compared. In both puppies and adults, the lesions were exudative and proliferative in the first two weeks, showing highly variable content of leukocytes, fibrin, erythrocytes, and edema fluid in the primary foci. A few in each age group showed confluent bronchopneumonic lesions. After the first two-week period, most lesions became solid dense granulomas, differing only in size, sharpness of delineation, and degree of caseation. In general, the size of the primary lesion at any stated age was roughly proportional to the size of the dose except that, after a period of about three months, the maximal size of most of the lesions had been reduced in various degrees by resolution and fibrous contraction.

### *Caseation in Primary Lesions*

In the primary pulmonary lesions of the mature dogs, coagulative necrosis was observed as early as 10 days but true caseation only after an elapse of 14 days from the time of injection. The pulmonary lesions in the puppies showed coagulative necrosis by the fifteenth day and caseation was first observed in a puppy killed with ether on the forty-first day. The comparison is not a parallel one since there were only 12 puppies which were examined within the first 50 days after injection and only three within a 15-day period as compared with 24 mature dogs examined within a 50-day period and 10 within 15 days.

The period during which caseation reached its greatest incidence and maximal extent was about the same in puppies and mature dogs, 40 to 90 days. Caseation persisted in the primary lesions of some of the puppies for at least 607 days and for 350 days in older dogs. In table 2 the incidence of caseation is compared in the three age groups. Six (40 per cent) of the youngest group showed caseous primary lesions compared with 2 (16.6 per cent) of the group of older puppies and 17 (32.1 per cent) of the mature dogs. When, instead of comparing each of the groups of puppies with the group of mature dogs and with each other, the figures for the two groups of puppies were combined, the incidence of caseation in primary lesions was 8 in the total of 27 puppies, or 29.6 per cent, as compared with 32.1 per cent in the adult dogs.

### *Cavitation*

In the 15 puppies of the first group (excluding three receiving 25 mg. doses) cavities were found in the primary lesions in 3 (20 per cent). Two died of progres-

sive tuberculosis, one after 90 days and the other 1,041 days after injection. In the first, infected by injection of 1.0 mg. of tubercle bacilli, the principal pulmonary lesion consisted of a partly solid and partly excavated lesion occupying the entire right basal lobe. The solid granulomatous tissue contained large areas of necrosis and a mass of caseous substance, lightly infiltrated with lime salts and forming part of the lining of the multilocular cavity. The rest of the lining of the cavity was formed by granulation tissue 1.0 to 4.0 mm. thick. There were small bronchopneumonic lesions containing acid-fast bacilli in the apical and middle lobes of the right lung. The kidneys, liver, and spleen contained epithelioid cell tubercles.

The second dog survived 1,041 days and showed much more complex lesions. The site of the primary focus in the right apical lobe was marked by an extensive, contracted pleural scar and adhesions. In the parenchyma there was a nonencapsulated, caseous granuloma containing a ragged cavity (13 by 8.0 by 2.0 mm.). The cavity was apparently of recent origin and was partly collapsed due to pleural effusion (Plate III, figure 1). Chronic renal tuberculosis with pelvic concrement was apparently a contributing cause of death.

The third was sacrificed after 607 days and showed an inactive cavity, 7 mm. in diameter, encrusted with lime salts (Plate II, figure 4).

Of the lesions of the 12 puppies of the older group, cavities occurred in two. Both were in puppies that had survived for long periods, 1,373 and 1,463 days, and both were completely inactive lesions.

The earliest lesion in a mature dog which showed cavitation was in a dog killed with ether 27 days after injection of 1.0 mg. of tubercle bacilli. The lesion was a relatively large one (7.0 by 5.0 by 3.5 cm.) and showed extensive coagulative necrosis but no true caseation. Twenty of the 53 adult dogs (37.7 per cent) showed some degree of cavitation of their primary lesions, varying from the largest (6.0 by 5.0 by 4.5 cm.) down to cavities only a few millimeters in diameter. The lesions showing extensive cavitation in this group of dogs invariably followed the injection of larger doses of bacilli (5.0 to 10 mg.). In 4 dogs, sacrificed after 210 to 343 days, the cavities were lined by smooth thin membranes and the lesions were completely healed in spite of the fact that in 3 of them the dosage was relatively large (4.0 or 5.0 mg.). The only other dog that showed a completely healed cavity was one sacrificed 93 days after injection of 1.0 mg. of tubercle bacilli. The cavity measured 15 mm. in maximal diameter.

### *Calcification in Primary Lesions*

Deposits of lime salts in the pulmonary lesions varied from fine granular precipitates in the caseous masses, recognizable only by microscopic examination, to solid chalky foci or, in the late stages, coarse, sand-like deposits imbedded in scar tissue. There were no instances of single, completely calcified, spherical nodes such as those frequently seen in the human lung. No evidence of ossification has been seen in the lesions of any of these dogs. The earliest lesion in which calcific substance was found was in a puppy injected with 0.2 mg. of tubercle bacilli at the age of three months and dead from tuberculous bronchopneumonia

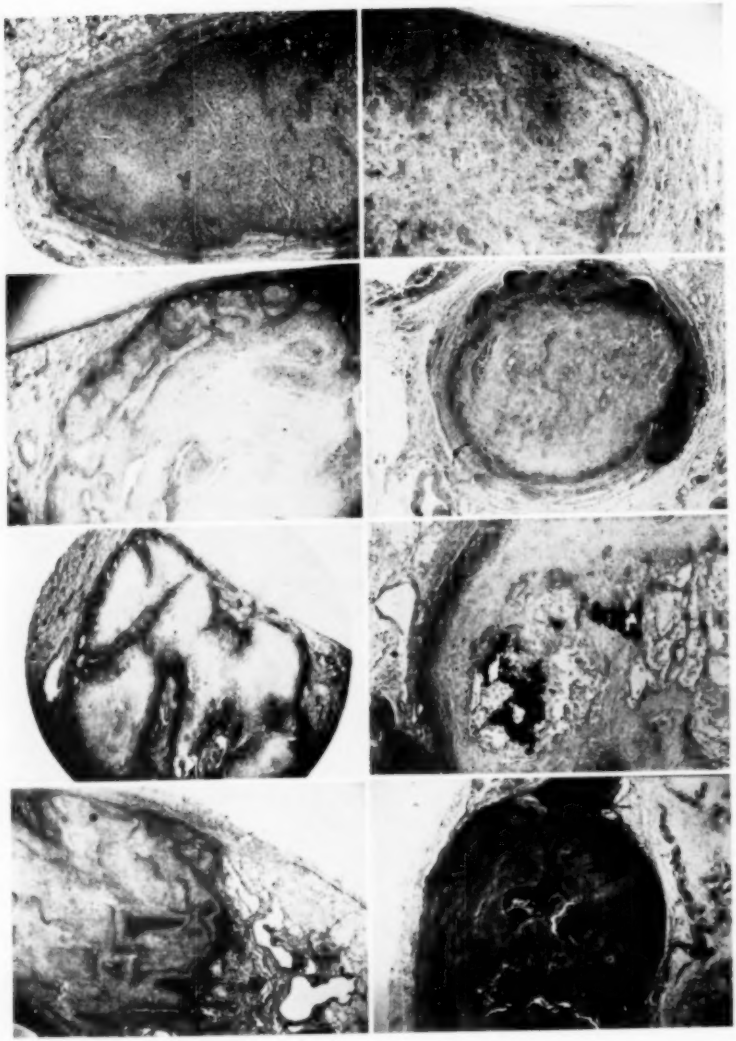

PLATE I

Photomicrographs of sections from primary pulmonary foci and lymph nodes. Stain: hematoxylin and eosin.

FIG. 1. (Upper left) Encapsulated primary lesion in dog No. 147, 5 months old at time of injection and dead of tuberculous bronchopneumonia 29 days after intrabronchial inoculation of 5.0 mg. of tubercle bacilli. X 12.5.

FIG. 2. (Upper right) Primary pulmonary focus in dog No. 144, 5 months old at time of injection. Dose 5.0 mg. X 12.5.

18 days afterward. The lesion was in the form of confluent bronchopneumonia with several centers of coagulative necrosis. The calcium deposits were located in the area of necrotic exudate (Plate II, figure 1).

In the puppies of group 1, ten primary foci (66.6 per cent) contained deposits of calcium salts. In group 2, there were three (25 per cent) and in group 3 (adults), only two (3.8 per cent) animals with calcium deposits in the foci. In group 2, the lesions were 162, 540, and 1,463 days old (Plate I, figures 7 and 8; Plate III, figures 5, 6, and 7). In group 3, the lesions were 223 and 350 days old. Both of the latter were encapsulated caseous nodules and the lime salts were deposited chiefly at the periphery of the caseous masses (Plate I, figures 3 and 5; Plate II, figure 2).

### *Lymph Nodes*

*Hypertrophy and hyperplasia:* Since no measurements were available for the normal tracheobronchial lymph nodes in dogs of different ages, arbitrary standards were used. It was found that the products of the principal diameters in millimeters of the lymph nodes of normal adult dogs usually fall below 250. Accordingly, this figure was used as the high limit of normal for both adults and puppies and only the figure for the largest single lymph node was used in the comparison. The product of the three diameters, if less than 250, was tabulated as minus; if between 250 and 1,250, as one plus; 1,250 and 2,500, 2 plus; 2,500 and 5,000, 3 plus; and over 5,000, 4 plus.

In comparing degrees of hyperplasia, as indicated by the extent of epithelioid cell transformation in microscopic sections, only the node showing the most advanced involvement (almost always the largest node) was used for comparison. The estimate of the percentage of the total area involved was expressed as follows: less than 25 per cent, one plus; 25 per cent to 50 per cent, 2 plus; 50 per cent to 75 per cent, 3 plus; and over 75 per cent, 4 plus. Sections were

FIG. 3. (Upper center left) One of two sharply circumscribed caseous foci in the right lung of a young dog (No. 128), sacrificed 223 days after receiving a dose of 6.0 mg. Both pulmonary foci were slightly calcified. X 10. (See also Plate II, figure 2.)

FIG. 4. (Upper center right) Caseous lymph node from mediastinum of dog No. 127, which died from tuberculous empyema following perforation of a subpleural focus on the sixty-third day after infection. Dose 3.0 mg. The dark fleck in the left margin of the caseous center is an accumulation of leukocytes. X 15.

FIG. 5. (Lower center left) Lobulated subpleural caseous focus in the right middle lobe, dog No. 121, sacrificed 350 days after injection of 5.0 mg. of tubercle bacilli. Fine granules of calcium salts were present in the caseous portions of the principal focus but none in the lymph nodes. The capsule is well defined but thin. X 8.5.

FIG. 6. (Lower center right) Caseous calcified tracheobronchial lymph node in puppy No. 171, dead of generalized tuberculosis 106 days after inoculation with 25 mg. A part of the necrotic tissue has been absorbed, leaving cystic spaces. X 25.

FIG. 7. (Lower left) Subpleural caseous primary focus in puppy No. 143 sacrificed 162 days after inoculation. Age at time of inoculation, 164 days. Dose 3.0 mg. The calcium deposits are in the form of thin laminae, roughly parallel with the peripheries of the fused caseous foci. X 12.5.

FIG. 8. (Lower right) Tracheobronchial node of puppy No. 143. The nodes were granulomatous and the calcium deposits (black) were surrounded by necrotic tissue. X 12.5.

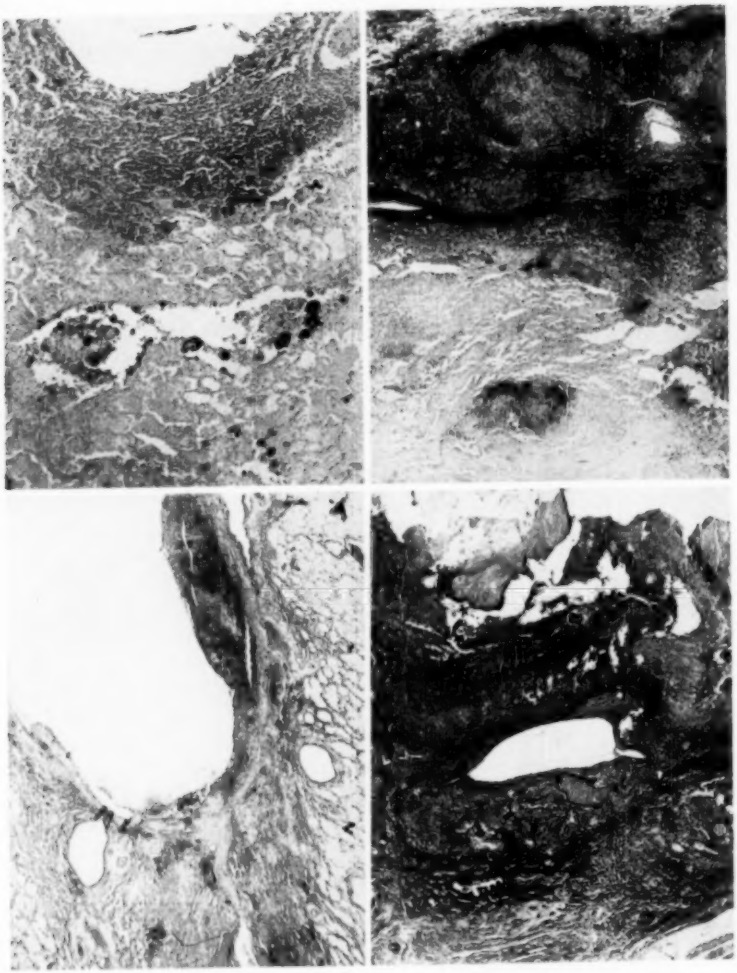

PLATE II

FIG. 1. (Upper left) Acute tuberculous bronchopneumonia in puppy No. 105, dead 18 days after intrabronchial inoculation. Age at time of infection, 12 weeks. Dose 0.2 mg. Bronchial epithelium is desquamated and the bronchial wall densely infiltrated with inflammatory cells. The surrounding necrotic parenchyma contains many granules of calcium salts. Early liquefaction with cavity formation is evident. X 80.

FIG. 2. (Upper right) Small focus of calcified caseous tissue (lower one-half of figure) in primary pulmonary focus of dog No. 128. Course, 223 days. X 37. (See also Plate I, figure 3.)

FIG. 3. (Lower left) Small cavity lined by tuberculous granulation tissue in dog No. 116, sacrificed 350 days after inoculation with 8.5 mg. of tubercle bacilli. This cavity communicated with a small bronchus in the right caudal lobe. X 20.

taken as near the middle of the lymph node as possible. The same method was used for estimating and expressing the extent of caseation.

Epithelioid cell transformation was seen in the earliest stages of infection (8 days in this material) and was observed to increase and wane with the intensification and decrease of inflammatory activity in the pulmonary lesion. Measurable hypertrophy, by the method used, was observed first by the fifteenth day in the puppies and by the tenth day in the older dogs. The degrees of hypertrophy and hyperplasia paralleled each other closely except in group 1 where the degree of hypertrophy was slight. This may be partly a consequence of the use of an inaccurate standard necessitated by the lack of available measurements of nodes in normal puppies. The high percentage of enlarged nodes and the greater degree of hypertrophy which was observed in the puppies of group 2 may have resulted from the fact that a greater proportion of this group received doses of tubercle bacilli in the higher ranges (3.0 to 5.0 mg.). In this group especially, there appears to be a direct relationship between the size of the dose, the size of the nodes, and the extent of epithelioid cell transformation.

The percentage of lymph nodes which showed some degree of epithelioid cell transformation was very nearly the same in the three groups, 73.3 per cent, 75 per cent, and 71.7 per cent, respectively. In a comparison of the number of nodes showing more extensive involvement (3 plus or 4 plus), however, it was noted that the nodes of the puppies, as a whole or as separate groups, were involved to this extent about twice as frequently as the nodes of the adults (59.3 per cent and 32.1 per cent, respectively).

*Caseation in lymph nodes:* While caseation was observed to be exceptional in the hilar lymph nodes as early as 14 days after the time of inoculation, usually true caseous necrosis was delayed for several weeks. The period during which caseation of nodes was found most frequently was between 43 and 61 days in mature dogs, but there was one instance as early as 14 days and one as late as 350 days. In the puppies, the earliest observation of caseation was at 25 days and the latest was in a still active lesion after 1,041 days. Both of these dogs died of tuberculosis. Comparison of the number of dogs in each group which showed caseous nodes at autopsy indicated a more frequent involvement in group 1 (40 per cent as compared with 33.3 per cent in group 2 and 26.4 per cent in group 3). The extent of caseous involvement, however, was greatest in group 3 and least in group 1. Coagulative necrosis as distinguished from true caseation was more frequently observed and more extensive in group 2.

*Calcification of lymph nodes:* There was only one instance of chalky deposits in the tracheobronchial lymph nodes of any of the 53 adult dogs in this series. Moreover, in a total of about 170 dogs examined for lesions after single or repeated injections of tubercle bacilli into the lung, this animal is the only mature

FIG. 4. (Lower right) Wall of cavity in apical lobe of puppy No. 157, sacrificed 607 days after inoculation. Dose 1.0 mg. Irregular chalky deposits are present in the granulomatous tissue around a bronchiole (center) and partly line the small cavity at the upper part of the figure. X 35.

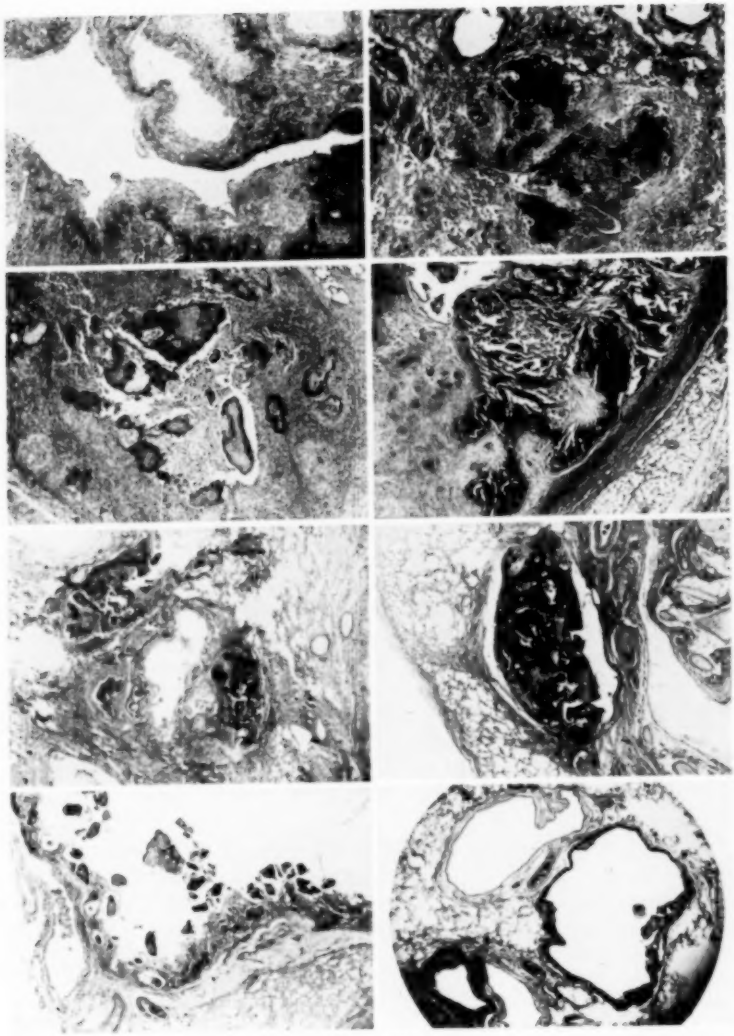

PLATE III

FIG. 1. (Upper left) Cavity formation in right apical lobe of puppy No. 170, dead of tuberculous empyema 1,041 days after injection. Dose, 5.0 mg. X 25.

FIG. 2 (Upper right) Subapical calcified granulomatous lesion in puppy No. 168, dead 86 days after inoculation. Dose, 1.0 mg. Pleural adhesions were present at apex. X 25.

FIG. 3. (Upper center left) Calcified tracheobronchial node in No. 168. X 25.

FIG. 4. (Upper center right) Well encapsulated calcified caseous node in puppy No. 171. Dose, 25 mg. Death from generalized tuberculosis 106 days after injection.

dog which exhibited such deposits at necropsy. The incidence in the entire material therefore is less than 1 per cent.

The puppies of group 1 showed six instances (40 per cent) of calcification of nodes and those of group 2, three instances (25 per cent).

*Hematogenous Lesions*

In order to gain some information concerning the relative frequency of lesions which were the result of hematogenous dissemination, the incidence of identifiable (by microscopic examination) tuberculous lesions in kidneys, liver, and spleen was tabulated and the values for the three groups of experimental animals were compared. The incidence was least in group 1, in which lesions of one or more organs appeared in 4 animals (26.6 per cent); three times in the kidneys, three times in the liver, and twice in the spleen. In group 2, hematogenous lesions were found in 6 animals (50 per cent); once in the kidney, five times in the liver, and five times in the spleen. Of 48 mature dogs in which microscopic sections of the kidneys, liver, and spleen were available, 28 (58.3 per cent) showed specific lesions in one or more of these organs; fourteen times in the kidneys, twenty-seven times in the liver, and ten times in the spleen. No attempt was made to differentiate between minimal and extensive lesions. In the great majority of instances, the lesions consisted of epithelioid cell tubercles of microscopic size. Some of the renal lesions were extensive and of long standing. It is probable that many more very small lesions could have been found by careful systematic examination of a large number of microscopic sections from each organ. In most animals, sections from only two or three blocks of each organ were prepared and examined, and in some cases only one. When lesions were not visible on macroscopic inspection, the tissue blocks were selected at random.

Before correction for the factor of dosage, the group of younger puppies showed hematogenous foci in 26.6 per cent as compared with 58.3 per cent in mature dogs. When only the dogs which received 1.0 mg. doses in these two groups were compared, the puppies show an incidence of 2 out of 8 (25 per cent) as compared with 8 out of 18 (44.4 per cent) adult dogs in which microscopic sections were available. In group 2 the only comparison which could be made between animals which received similar doses was in those which received larger doses of bacilli (3.0 to 7.0 mg.). The percentage of animals in each group which showed hematogenous lesions after receiving doses within this range were: in group 2, 4 out of 7 (57.1 per cent); and in group 3, 18 out of 26 (69.2 per cent).

FIG. 5. (Lower center left) Calcified granulomatous and fibrous lesions around the terminal part of stem bronchus of left basal lobe. Puppy No. 107, dead of ruptured tuberculous aneurysm of aorta 540 days after inoculation. Dose, 0.4 mg. All pulmonary lesions were inactive. X 12.5.

FIG. 6. (Lower center right) Solidly calcified nodule in areolar tissue attached to pleura of puppy No. 107. X 12.5.

FIG. 8. (Lower left) Calcified lining of small encapsulated cyst in lung of puppy No. 106, sacrificed 1,463 days after inoculation. X 12.5.

FIG. 8. (Lower right) Calcified lining in healed cystic pulmonary lesion of puppy No. 159, sacrificed 608 days after inoculation of 1.0 mg. dose. X 12.5.

## DISCUSSION

Since the purpose of this analysis was to ascertain whether or not differences could be demonstrated between the lesions resulting from the intrabronchial inoculation of tubercle bacilli in dogs of different ages, the discussion will be confined to comparisons between them. No significant differences were found in mortality rate in the three groups when dosage was taken into consideration, and this was true whether the comparison was made among dogs receiving similar total doses per individual or on the basis of dosage per kilogram of body weight. The factor which was most important in determining mortality rate in these experiments, as in previously reported data from a larger number of dogs (4), was the size of the dose. Comparison of the structure of the lesions in these three groups of dogs necessitated the conclusion that the evolution of tuberculous lesions was fundamentally the same at different ages of the animal since there were more similarities than differences. The promptness and intensity of the inflammatory response, as indicated by the size of primary foci and extent of necrosis, were so nearly the same that the differences can be explained on the basis of individual susceptibility and of variations in site of injection. There were only a few puppies which were sacrificed during the earlier stages of development of their pulmonary lesions, so that it was not possible to determine in this material whether or not caseation regularly occurred earlier in adult dogs than in puppies. It is reasonably certain, however, that in both age groups the maximal extent of caseation in the primary focus occurred at about the same time, that is, between forty and ninety days.

The tendency to cavity formation in pulmonary lesions in puppies appeared to be significantly less than in adults. In each group of puppies and in the two groups of puppies as a whole, the incidence of cavity formation was approximately one-half of that in the adult dogs. This difference was not adequately explained on the basis of data assembled from the present material. If the lesions of all of the experimental animals had been examined at about the same stage of development, for example, two or three months after the time of injection, a correlation between the extent of necrosis and cavity formation might be expected. Since this was not the case, several of the cavities observed at necropsy were part of healed residues and therefore no necrotic tissue remained in the lesions. This would, in part, explain the lack of correlation between the frequency of occurrence of caseation and of cavitation in the three groups of dogs. Furthermore, it was found that in rapidly progressive lesions with cavities, simple coagulative necrosis in surrounding tissue was present in many cases where true caseation was not observed. This was true in 7 of the 20 dogs of group 3 which showed cavities in the lung. The cavities found in the two puppies of the older group were completely healed. The cavities in 3 of the younger puppies were found in an active, progressive state. In the mature dogs, five of the twenty primary lesions with cavities were entirely healed. It is evident that excavated lesions may heal spontaneously in either puppies or in adult dogs. The size of the cavities was dependent to an important degree upon the size of the infecting dose for, in the older group of dogs, the formation of the largest cavities in-

variably followed the injection of larger doses (5.0 to 10 mg.) of tubercle bacilli. Since the size and extent of the lesions in the three groups were about the same and the frequency and extent of caseation were greater in the younger group of puppies, apparently no close correlation exists between the incidence of caseation and of cavitation. Moreover, there was no evidence of a correlation between cavity formation and the degree of hypersensitivity as indicated by cutaneous reactivity to tuberculin.

The only anatomical difference which might possibly have some bearing upon the tendency to form cavities is the greater rigidity of the bronchial walls of adult dogs. In puppies, as in human infants and children, the smaller bronchi tend to collapse, become occluded by inspissated exudate, and thus seal off the lesion from the bronchial tree. In adults a maintenance of the patency of the bronchial lumen provides for the escape of necrotic tissue and exudate and supplies oxygen for the more rapid growth of the mycobacteria.

No unequivocal differences in degree of involvement of lymph nodes of puppies, as compared with those of adults, were observed when the criteria of hypertrophy and epithelioid cell hyperplasia were used. Caseation, on the other hand, appeared to occur more readily in younger puppies than in older puppies or in mature dogs. The numbers involved in each group, however, were too small to be statistically significant. The incidence and extent of involvement by caseous necrosis of the tracheobronchial lymph nodes were related more closely to the size of the infecting dose than to the age of the animals. It is certain that the drainage lymph nodes are always involved to some extent so long as there is an active lesion in the pulmonary parenchyma.

The most striking difference between the lesions of dogs of different ages was the much greater tendency of necrotic lesions to calcify when they occurred in puppies, especially of the youngest group. This phenomenon was not dependent upon the frequency or extent of caseation since the group differences in degree or incidence of caseation in primary lesions were not great. For example, the incidence of caseation in primary foci of group 1 was 40 per cent as compared with 32.1 per cent in group 3, while 66.6 per cent of the lesions of group 1 contained calcified foci as compared with 3.8 per cent in group 3.

In group 1, calcification in some degree was present in either the primary focus or drainage lymph nodes, or both, in every puppy with an infection as old as 57 days. Four of the 12 puppies of group 2 showed calcareous foci in some part of the primary complex, and of the mature dogs only 3 of the 53 showed calcareous foci in either lymph node or pulmonary lesion, never in both. Two of these foci were so small that they were found only by examination of microscopic sections. Of the 2 which showed chalky foci in the primary lesions, one was a young dog which grew rapidly, almost doubling its weight during the 228-day course of the experiment, so that it would seem reasonable to consider it an older puppy rather than a fully mature dog.

Even in the absence of true caseation, some of the necrotic foci in a few of the puppies contained finely granular "clouds" of calcium salts and these appeared as early as 18 days after the time of injection (dog No. 105). Since it is

not likely that the chemical constitution of the tuberculous foci in animals of various ages differs greatly, the explanation can be looked for in the more active metabolism of calcium in the youngest puppies. The concentrations of both calcium and inorganic phosphate in the blood of normal young puppies are consistently higher than in adult dogs (ca: approximately 11 to 12.5 mg. per 100 cc. in puppies; 9.5 to 11 mg. per 100 cc. in adult dogs; P: 5 to 6 mg. per 100 cc. in puppies; 3.5 to 4.5 mg. per 100 cc. in adults (5). The values for calcium and inorganic phosphate are very nearly the same as the above in human infants and adults. Consequently, if the present interpretation is correct, these age group differences in the tendency of tuberculous lesions to calcify may have an important bearing upon our views of the fate of caseous lesions in the lung and lymph nodes of human beings, and upon our interpretation of observed anatomical differences between lesions in children and in adults.

Usually it is assumed that, in the adult with tuberculous infection of the lungs, the lymph nodes show little or no involvement because of a supposed specific or nonspecific immunity acquired during childhood. This apparent immunity of lymph nodes to tuberculous infection has been shown to exist for primary infections in adults also. Sweany (6) considers it a natural characteristic of adult tissues and not necessarily related to acquired specific immunity. It is possible, in fact probable, from the evidence presented above, that the explanation of this phenomenon lies in the relatively slight tendency for the lesions to calcify. Uncalcified caseous lesions are gradually absorbed and replaced by scar tissue over a period of months or years while a calcified or ossified lesion may persist for life. Thus in primary lesions acquired during childhood, caseous complexes are found if examined in the early stage, or calcified complexes if examined later; while in those acquired during adult life, caseous lesions are found in the transient early stage (and therefore infrequently in necropsies) and only nonspecific scars in the later stages. This does not imply that calcification does not occur in the lesions which develop during adulthood, but only that calcification is much less frequent and less extensive in adults than in childhood and therefore leads only infrequently to calcified residues.

The frequent occurrence of hematogenous lesions in liver, spleen, and kidneys in the presence of active, extending tuberculous lesions in the lung and lymph nodes and the tendency of such lesions to regress spontaneously are well known in tuberculosis of human beings, but infrequently seen except in the tissues from fatal cases. It is usually assumed that such lesions are more common in progressive primary infections of infants and young children than in the more slowly developing and progressing infections of adults. The observation in these experiments that minimal hematogenous lesions were approximately twice as frequent in mature animals as in the youngest group, although the mortality rate is not significantly greater, would suggest that these lesions are of little importance in the determination of the outcome of the infection. They usually represent the result of a transient bacteremia and tend to disappear without leaving a recognizable residue.

## SUMMARY AND CONCLUSIONS

1. In a comparison of susceptibility to tuberculous infection in younger puppies, one and one-half to three months old; in older puppies, five to eight months old; in and mature dogs, no significant differences were found in mortality rate when comparable doses of virulent tubercle bacilli were administered by the intrabronchial route. Likewise no significant differences in suscepibility were observed when the mortality from tuberculosis in the puppies of both age groups was compared with the mortality of mature dogs.

2. The size of the pulmonary lesions and their form and cellular composition in the early stages of development were essentially the same in younger puppies, older puppies, and mature dogs.

3. Cavity formation at the site of the primary pulmonary lesions was about twice as frequent in mature dogs as in either of the groups of puppies.

4. The incidence and extent of caseation of primary foci and of tracheobronchial lymph nodes did not differ significantly in a comparison of puppies and adult dogs. The maximal extent of caseation in the primary complex in all three age groups was reached within a period of forty to ninety days after the time of infection.

5. Calcification of the tuberculous lesions of the lungs was much more frequent in the younger puppies (66.6 per cent) than in the older puppies (25 per cent) or in mature dogs (3.8 per cent). There was no correlation between the frequency and extent of caseation and the incidence of calcification for reasons discussed. A similar difference in incidence of calcification of caseous lesions of lymph nodes was observed when lesions of dogs in the three age groups were compared.

6. The presence of epithelioid cell tubercles in the liver, spleen, and kidneys during the stage of active progression of pulmonary infections was about twice as frequent in puppies of the older age group and in adult dogs as in the younger puppies. These lesions are considered to represent the effects of transient bacteremia, usually disappearing without trace as the central lesion becomes arrested, or of a terminal bacteremia. As was to be expected, the incidence of hematogenous lesions was greater in those dogs which died of progressive tuberculosis than in those which were sacrificed during various stages of development and regression of their pulmonary lesions. The incidence of hematogenous lesions showed no correlation with the mortality rate, however, when a comparison was made between the animals of the three age groups.

## SUMMARIO Y CONCLUSIONES

### *Tuberculosis Pulmonar Experimental en el Perro. Comparaciones de las Lesiones en los Cachorros y los Perros Maduros*

1. En una comparación de la susceptibilidad a la infección tuberculosa de los cachorrillos de uno y medio a tres meses de edad; los cachorros más viejos, de cinco a ocho meses; y los perros maduros, no se notaron diferencias significativas

en la tasa de mortalidad al administrar dosis comparables de bacilos tuberculoso virulentos por vía intrabronquial. Tampoco se observó mayor diferencia en la susceptibilidad al comparar la mortalidad tuberculosa en los cachorros de ambos grupos etarios con la de los perros maduros.

2. El tamaño de las lesiones pulmonares y su forma y composición celular en las primeras etapas de desarrollo fueron en el fondo idénticas en los cachorros más jóvenes y los más viejos y los perros maduros.

3. La formación de cavernas en el sitio de las lesiones pulmonares primarias fué aproximadamente doble en los perros maduros que en uno u otro de los grupos de cachorros.

4. La incidencia y extensión de la caseación de focos primarios y de ganglios linfáticos traqueobronquiales no varió significativamente en una comparación de los cachorros y los perros adultos. La caseación en el complejo primario alcanzó su extensión máxima en los tres grupos etarios en término de cuarenta a noventa días de la fecha de la infección.

5. La calcificación de las lesiones tuberculosas de los pulmones fué mucho más frecuente en los cachorros más pequeños (66.6 por ciento) que en los mayores (25 por ciento) o en los perros crecidos (3.8 por ciento). No hubo correlación entre la frecuencia y extensión de la caseación y la incidencia de calcificación por las razones expuestas. Observóse una diferencia semejante en la incidencia de calcificación de los ganglios linfáticos al comparar las lesiones en los tres grupos de perros.

6. Los tubérculos de células epitelioideas del hígado, bazo y riñones durante el período de avance activo de las infecciones pulmonares alcanzó una frecuencia aproximadamente doble en los cachorros mayores y los perros adultos que en los cachorros más pequeños. Esas lesiones pasan por representar los efectos de una bacteriemia pasajera, desapareciendo generalmente sin dejar trazas a medida que se estaciona la lesión central, o de una bacteriemia terminal. Como era de esperar, la incidencia de lesiones hematógenas fué mayor en los perros que murieron de tuberculosis evolutiva que en los sacrificados durante varias etapas de desarrollo y regresión de sus lesiones pulmonares. No obstante, la incidencia de lesiones hematógenas no reveló correlación con la tasa de mortalidad al trazar una comparación entre los animales de los tres grupos etarios.

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# STUDIES ON THE CONTAGIOUSNESS OF COCCIDIOIDOMYCOSIS[1]

## II. The Fate of Spherules in Sputum Exposed Out of Doors

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### INTRODUCTION

The present report is the second in a series of studies that emphasize the contagiousness of coccidioidomycosis. In the first report (1) it was shown that spherule-containing exudates of man or guinea pig when instilled intratracheally in guinea pigs produced localized lesions in the lung which simulated the common human form of infection. It was also demonstrated that spherules in exudates from human sources, when kept at refrigerator temperatures (10° to 15° C.), remained viable and infectious and did not produce hyphae or chlamydospores for the 110 days of the experiment.

In the present study an investigation was made of the fate of spherules in 52 sputum collections which were divided into 80 samples and were exposed out of doors under varied conditions. These conditions included mixing with earth and exposure to the sun or shade out of doors. A limited number of specimens were kept in the icebox and the incubator. Of necessity, 38 of the 52 collections were from one patient who had a recurrent cavity in one apex about 2.0 cm. in diameter. Although spherules were observed in about one-half of the samples from this patient, it was difficult to culture them. During the course of the study, the patient in question recovered, with roentgenographic evidence of closing of the cavity. These features of the case are important because they probably influenced the viability of the spherules.

*Coccidioides immitis* has been cultured from soil (2) but the phase of the fungus as it existed in the soil was not determined. There seems to be a general agreement that the fungus does not propagate in the soil, although it is disseminated in dust (3). As far as the writers are aware, this is the first study where the role of the soil has been explored as a possibility of fungus growth.

### METHOD

Sputum specimens were collected for twenty-four hours and brought immediately to the laboratory. The samples were mixed thoroughly and examined in the following manner:

1. A few drops were placed in a similar volume of 10 per cent sodium hydroxide in 5 per cent glycerin on a glass slide and covered with a cover slip; after one hour or more, microscopic examinations were made.
2. From 3.0 to 5.0 cc. of the sputum were placed on each of the three Petri plates of 3 per cent tryptose agar adjusted to a pH of 3.5. The plates were allowed to stand at room temperature over night to absorb some of the liquid and then were incubated at about 30°C.
3. Other aliquots were divided into 10 ml. amounts and placed in sputum cups. One-half

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of the samples were mixed with equal volumes of soil from the area (sandy, reddish-tan Santa Fe soil). The cups were covered with clear X-ray film and sealed with broad bands of adhesive tape. The boxes were placed on window sills out of doors about four feet off the ground in areas with direct sun or in areas with the most shade. A few samples were placed in Petri dishes and put in an incubator (30°C.) while others were placed in test tubes in the refrigerator. At regular intervals from one to 240 days, specimens were taken from the boxes by means of needle and syringe without opening the box. Five to 10 ml. of saline were first injected on the surface of the box content and the mixture allowed to stand from five to fifteen minutes with constant agitation. The removed suspensions were examined by direct amount in 10 per cent sodium hydroxide, cultured on 3 per cent tryptose agar and, in some instances, 1.0 to 2.0 ml. were injected intraperitoneally in guinea pigs. When spherules were seen microscopically, 0.2 ml. were instilled intratracheally by a method described previously (2) in a limited number of animals.

All cultures were kept for two to three weeks before discarding and animals were killed, as a rule, three to eight weeks after inoculation. Suspicious lesions were examined directly with sodium hydroxide, cultured, and microscopic sections made.

## RESULTS

### *Gross Findings*

Usually the specimens were dried after ten to fifteen days, but some were dried as early as four to five days, while others not until three weeks or more. In most instances where soil was used, a gray powder-like film or flakes formed over the surface. This finding was not necessarily associated with the recovery of spherules or hyphae of *Coccidioides immitis* or of other fungi. The sputum specimens which were not mixed with earth dried after similar periods of time, as above, usually becoming flaky or scaly; the color depended more or less upon that of the original specimen.

### ORIGINAL SAMPLES

There were 80 original samples cultured on 240 Petri plates immediately upon being received in the laboratory. Of these, 44, or little better than one-half, contained spherules on direct examination. None of the samples showed hyphae, and 10, or 12.25 per cent, yielded positive cultures. This is a low percentage in proved cases of coccidioidomycosis. The explanation lies in the fact that 38 of the 52 collections were from one patient who had a minimal lesion with several remissions and exacerbations, and who finally recovered clinically, with closure of 2.0 cm. cavity. Three other patients were used, but their sputum yield per day was small.

On several occasions, spherule counts were made of the sputum. In the patient from whom most of the specimens were obtained, the count averaged from 525 to 650 per ml. of sputum. Four separate counts were made of each specimen, first treating with 10 per cent sodium hydroxide in 5 per cent glycerin for eighteen hours and then counting in a Neubauer counting chamber.

The results obtained with the fresh original specimens must be borne in mind when evaluating the findings in the remainder of the experiment. In the table, each category lists the original number of specimens and the number of speci-

mens that were examined at the time intervals given. For example, when spherules are listed at one time interval and not at another, or vice versa, it does not necessarily mean that in a particular specimen the disappearance or appearance of spherules took place. It is possible that a different specimen is involved. Two hundred and seventy-four examinations were made of the 80 samples.

*In the Shade*

*With earth:* Of the original 18 specimens examined, 10, or 55.6 per cent, revealed spherules; 2, or 11.1 per cent, gave positive cultures. In one sample that

TABLE 1

*Fate of Coccidioides Immitis Spherules Out of Doors*

| DAYS | IN SHADE | | | | | | | | | | | | IN SUN | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | With Earth | | | | Animals | | Without Earth | | | | Animals | | With Earth | | | | Animals | | Without Earth | | | | Animals | |
| | No. | S | H | C | No. | Pos. | No. | S | H | C | No. | Pos. | No. | S | H | C | No. | Pos. | No. | S | H | C | No. | Pos. |
| Original | 18 | 10 | 0 | 2 | — | — | 20 | 11 | 0 | 1 | — | — | 22 | 10 | 0 | 4 | — | — | 20 | 13 | 0 | 3 | — | — |
| ½ to 1 | 2 | 1 | 0 | 0 | — | — | 8 | 2 | 0 | 0 | — | — | 7 | 0 | 1 | 5 | — | — | 4 | 2 | 0 | 0 | — | — |
| 2 to 3 | 2 | 0 | 0 | 1 | — | — | 9 | 3 | 2 | 1 | — | — | 5 | 0 | 2* | 2 | — | — | 9 | 3 | 1 | 0 | — | — |
| 4 to 7 | 3 | 0 | 0 | 0 | — | — | 11 | 3 | 4 | 4 | 1 | 0 | 7 | 0 | 3 | 2 | 1 | 0 | 10 | 0 | 0 | 0 | — | — |
| 8 to 14 | 5 | 2 | 4 | 0 | — | — | 6 | 4 | 1 | 0 | — | — | 4 | 0 | 2 | 1 | 1 | 0 | 5 | 0 | 1 | 0 | 1 | 0 |
| 15 to 30 | 3 | 0 | 0 | 0 | 3 | 0 | 5 | 2 | 1 | 0 | 2 | 0 | 2 | 0 | 1 | 0 | 1 | 0 | 5 | 2 | 0 | 0 | 2+ | 0 |
| 31 to 89 | 4 | 2 | 0 | 1 | 4 | 0 | 4 | 0 | 0 | 0 | 2 | 0 | 5 | 1 | 0 | 0 | 4 | 0 | 4 | 2 | 0 | 0 | 4 | 2 |
| 90 to 179 | 7 | 4 | 0 | 0 | 4Δ | 1 | 11 | 7 | 0 | 0 | 10 | 2Δ | 5 | 4 | 0 | 0 | 3 | 0 | 6 | 5 | 0 | 0 | 4 | 1Δ |
| 180 to 240 | 1 | 0 | 0 | 0 | — | — | 1 | 0 | 0 | 0 | 1 | 0 | 6 | 2 | 1 | 0 | 1 | — | 7 | 5 | 0 | 0 | 2 | 0 |
| Totals | 45 | 19 | 4 | 4 | 11 | 1 | 75 | 32 | 8 | 6 | 16 | 2 | 63 | 17 | 10 | 14 | 11 | 0 | 70 | 32 | 2 | 3 | 13 | 3 |

S, Spherules; H, Hyphae; C, Culture positive; No., Number of specimens; 0, Negative; —, Not done; Pos., Positive.

* Cultures negative.

Δ Suggestive spherules.

+ Histology positive but no spherules.

yielded a positive culture, spherules were not seen on the original direct mount. Hyphae were noted in 4 specimens 8 to 14 days old. All had dried. In 3, a gray powder-like film covered the surface, while the fourth was not remarkable. Suggestive chlamydospores were seen in one and a germinating spherule was seen in another sample. Hyphae were not noted after 14 days, but spherules were found in 6 of 11 specimens 31 to 179 days old. In one such specimen endospores were seen, some of which were germinating. One culture was positive in a 72-day-old specimen in which no spherules or hyphae were noted on direct examination. The animal inoculated with this material unfortunately died in two days. An animal injected intraperitoneally with 1.0 cc. suspension of a 139-day-old specimen died thirteen days later. The lungs were hemorrhagic and there were small

abcesses in the peritoneum. A direct mount of the pus showed suggestive plasmolyzed spherules; the culture was negative. On direct examination of the material used for the animal inoculation, endospores (some germinating) were seen.

In summary, sputum mixed with earth and kept in the shade out of doors, revealed hyphae in specimens only after 8 to 14 days of exposure. After this time only spherules were noted. In one specimen 139 days old, germinating endospores were seen. This specimen produced intraperitoneal abscesses containing plasmolyzed spherules when injected into a guinea pig.

*Without earth:* In 20 original specimens, 11, or 55 per cent, contained spherules but no hyphae. One culture was positive. Hyphae were observed in 2- to 3-day-old specimens as well as at 19 days in one specimen. Spherules were present almost throughout. Cultures were positive in samples up to 7 days after exposure. It is of interest that at the 4- to 7-day period, 4 of 11 samples cultured were positive, or 36 per cent. In the material used for culturing corresponding to those positive on culture, hyphae were present in 3 on direct examination, and in one neither spherules nor hyphae were detected. There were no positive cultures after fourteen days. Two of the 16 inoculated animals presented lesions with suggestive spherules. One animal was injected intraperitoneally with a suspension of sputum 91 days old. This sputum originally contained spherules, but the culture was negative. Hyphae were seen at 48 hours, 72 hours, and the fifth, sixth, and seventh days after exposure. Cultures were positive on the fifth and sixth days of exposure. The actual 91-day-old material injected was negative on direct examination, as was the culture. The guinea pig sacrificed 8 weeks after inoculation presented yellowish-gray nodules in the spleen which were centrally soft and measured up to 4.0 mm. in diameter. Lymph nodes were enlarged up to 1.0 cm. in diameter. A direct mount made of the splenic nodules was negative, as were the cultures but, on sectioning the spleen, focal granuloma composed of epithelioid cells, giant cells, and central necrotic material with suggestive spherules were seen. Another animal was injected with 136-day-old sputum that originally yielded spherules on direct examination and a positive culture. Examination at 136 days by direct smear and culture was negative, but the guinea pig inoculated intraperitoneally developed numerous omental abscesses which on direct examination revealed plasmolyzed spherules. Culture of the abscess material was negative. The lungs were hemorrhagic, but the sections were negative for coccidioidomycosis.

In summary, sputum containing spherules exposed out of doors in the shade, without soil, presented hyphae in the 2- and 3-day-old specimens as well as in the 19-day-old specimen. No chlamydospores were seen. Spherules were noted at practically all times up to 90 to 179 days of exposure. Cultures were positive up to 4 to 7 days and were negative thereafter. Post-mortem examination of animals inoculated with 91- and 136-day-old sputum revealed lesions from which plasmolyzed spherules were observed on direct mount with sodium hydroxide. Cultures of the lesions were negative. The histologic picture of the spleen in one was highly suggestive of a coccidioidomycotic granuloma.

*In Sun*

*With earth:* Spherules were found on direct examination in 10 of the 22 original specimens used in this category. Four of the samples, or 18 per cent, grew on culture. Hyphae were noted in a 24-hour sample (figure 1), and this material grew on 3 per cent tryptose agar. Four other samples 6 to 24 hours old grew, although no hyphae were seen on direct mount. One 13-day-old specimen contained numerous hyphae and chlamydospores and grew on culture. Hyphae were

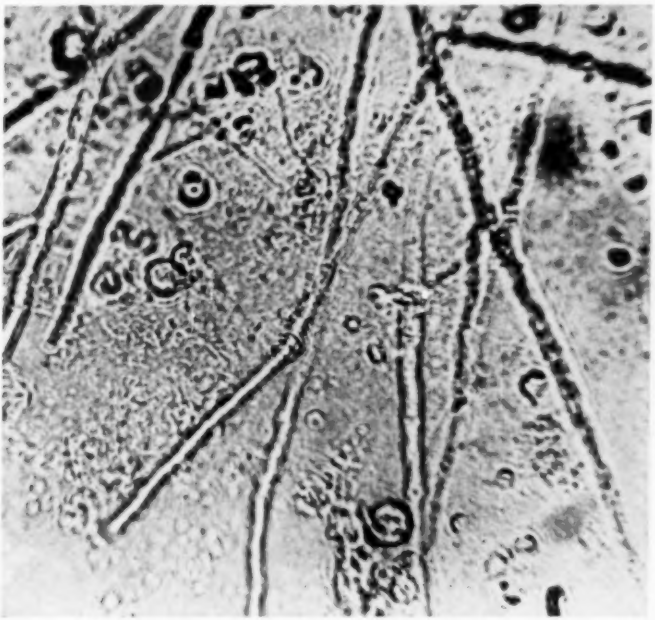

FIG. 1. Hyphae and endospores in direct mount of sputum mixed with earth and exposed to sun for twenty-four hours.

also seen in a 15-day-old specimen, but then not again until after 236 days of exposure. This specimen had racquet mycelia, but the culture was negative for *Coccidioides immitis* but positive for *Alternaria* and *Fusarium*. Spherules were not seen after 6 hours of exposure, but were again noted in an 84-day-old specimen when endospores were also seen. Eleven animals injected with material exposed for varying periods were essentially negative as determined by autopsy mounts, cultures, and microscopic sections.

In summary, in specimens of sputum mixed with earth and exposed to the sun, hyphae were noted at 24 hours and persisted for 15 days. In one specimen 13 days old, chlamydospores were seen which grew on culture. The cultures up

to 14 days were positive in a high percentage of examinations (10 of 23 samples, or 43 per cent). Spherules, on the other hand, were not seen after six hours, but were noted again in the 84-day sample or older. Animal inoculations of specimens older than 14 days were negative for coccidioidomycosis.

*Without earth:* Spherules were seen in 13 of the 20 original specimens (65 per cent). Hyphae rarely appeared (one at 48 hours and one at 9 days). Cultures remained negative throughout. Except for the period 4 to 14 days, spherules

FIG. 2. Spherule in sputum sample exposed to sun for seventy days (without earth).

were seen regularly and increased after 3 months (figure 2). Three of the 13 animals inoculated with resuspended material that was exposed for more than 7 days developed lesions that could be interpreted as coccidioidomycotic in character.

A review of the findings of these animals is as follows:

One animal was injected with 59-day-old spherule-containing sputum and treated with two parts of 0.05 per cent copper sulfate for 4 hours by the intratracheal route. When sacrificed 3 weeks later, a depressed indurated area in both upper lobes of the lungs could be seen. The hilar lymph nodes were enlarged up to 5.0 mm. in diameter. The spleen was larger than normal. Smears and culture of the lymph nodes were negative. Sections of the lung revealed

that the bronchi were filled with pus cells, as were the corresponding alveoli and peribronchial tissue. The most marked changes were those of interstitial character with granuloma formation and numerous giant cells of the Toulon and Langhans' type. In several of the giant cells, "ghosts" of what appear to have been spherules and one definite spherule were noted. Small abcesses were scattered throughout the lung with central core of pus cells and periphery of epithelioid cells and lymphocytes. Suggestive pale staining foreign bodies were noted at times. A second animal injected intraperitoneally with the same material died in 9 days. Smears and cultures of small nodules in the peritoneum were negative.

In an animal injected intraperitoneally with 71-day-old sputum, in which spherules were seen on direct mount, small dark plaques developed in the omentum 2 months after inoculation. On direct mount of these areas, one spherule was noted; cultures were negative. The mate to this animal injected with the same material intratracheally was not remarkable.

An animal injected intraperitoneally with 160-day-old material in which spherules were seen was killed after 3 weeks. In the lungs were several small dark areas of induration. The hilar lymph node was enlarged to 5 by 8 mm. in diameter. Direct mounts of the lung showed spherules suggestive of *Coccidioides immitis*, but the culture was negative.

Summary of results obtained by allowing sputum to remain in the sun without soil: Hyphae were rarely observed, although some of the specimens did not dry from 9 to 16 days after exposure. A few did dry by the third to fifth day. Spherules were almost always present except for the 4- to 14-day-old specimens. They were especially prevalent after 3 months of exposure. Cultures, however, were consistently negative, although 2 of the 13 animals injected developed lesions which were considered to be coccidioidomycotic in character. A third animal developed lesions which contained suggestive spherules, while in the fourth animal the histologic picture was considered positive but no spherules were noted.

### *Summary of Results*

Under the conditions of this experiment, specimens of sputum from known cases of coccidioidomycosis (55 per cent containing spherules but no hyphae), exposed out of doors in the shade without soil or exposed to the sun and mixed with soil, were found to contain hyphae after 24 to 48 hours. This phenomenon was seen very frequently up to 7 days, less frequently up to 15 to 30 days, and very rarely thereafter. Chlamydospores were seen in one instance. Cultures were frequently positive up to 4 to 7 days: 43 per cent in specimens exposed to the sun with earth and 14.7 per cent maintained in the shade without earth. On the other hand, specimens without earth left in the sun rarely presented hyphae. This was also true for the specimens in the shade with earth except for the 8- to 14-day samples which for some unknown reason gave a high percentage where hyphae were noted. In one of these specimens 14 days old, chlamydospores were seen but the cultures were negative. It may be added that the culture plates used at this time were of questionable value in supporting growth.

Spherules were seen more regularly throughout the experiment and especially after one month of exposure. There was one exception, however, in the specimens mixed with earth and exposed to the sun. In the latter, spherules were present in 45 per cent of the original specimens, yet were not seen after 6 hours, and remained absent in all specimens examined during 30 days of exposure, after which time they reappeared.

There was one positive culture after 30 days of exposure in the entire experiment. Animal inoculations of specimens 30 days old and older were positive in two and highly suspicious in four more ("ghosts" of spherules noted in the lesions).

To exclude the possibility that the spherules seen in the older specimens came from without or could have been in the soil proper, aliquots of sputum alone were kept in the icebox or in the incubator. Samples 158 days old kept at either temperature when examined contained spherules similar to those described in the specimens exposed out of doors. In the former, as well as in the latter, there were periods when samples failed to reveal spherules. Hyphae were never noted in the incubated or refrigerated samples.

The vegetative form of *Coccidioides immitis* was seen most frequently in sputum specimens kept out of doors and mixed with earth and exposed to the sun. Next in frequency were samples of sputum alone kept in the shade without soil. Spherules were seen most frequently in samples without earth and kept in the shade and least frequently when mixed with earth and kept in the sun. The out-of-door conditions in which both phases of the fungus were seen most frequently were in the shade without earth. In specimens kept in the sun without earth, neither phase of the fungus was seen very frequently, if at all. After 30 days, when practically all specimens had dried up, the vegetative form was rarely seen, but spherules were noted in a high percentage of specimens. These spherules were either well preserved or plasmolyzed, with definite refractile walls. Endospores were also seen. This was true for all types of exposures. The viability of the spherules in these samples was of a very low order.

## DISCUSSION

An attempt has been made to determine the fate of spherules in sputum exposed out of doors in a manner closely resembling their natural existence. It is hoped that other similar studies will be carried out in endemic areas where soil conditions are unquestionably different and may affect the viability of the spherules. It is recommended that sputum specimens be used which are rich in spherules and which yield a high percentage of positive cultures. The season of the year is also an important factor in that a possibility of propagation in a warm environment is greater than in a cold environment. The experiments here reported were performed between March and December, but the majority of experiments were done between April and October. This constitutes a period of warm temperatures in Santa Fe varying between 50° and 90°F.

With rare exception (4) only the parasitic phase of *Coccidioides immitis* is seen in man and animal. This phase is represented by spherule-like bodies from 10 to 60 microns in diameter having refractile walls and which on maturity contain numerous endospores. In the body the walls of the spherule become interrupted and the endospores are liberated. The latter are extremely difficult to identify on direct examination or in microscopic section of the tissues because of their thin walls (their size one to five microns), as they often blend in with the sur-

rounding structures. The endospores will develop into spherules in a proper environment. In exceedingly rare instances large pulmonary cavities may contain the vegetative stage of the fungus, namely, hyphae and cylindrical spores or chlamydospores (4). Except for this oddity, the vegetative stage has been described only from its appearance on culture media. Spherule-like bodies have been described on culture under special conditions, but these, too, are rare phenomena (5).

The fate of spherules or endospores after they leave the body has remained unsolved. Positive cultures have been reported from soil samples (2), but the stage of the fungus as it existed in the soil was not described. It has been stated that the spherules undergo a vegetative stage in nature after which time they become infective to man and animal (3). Where this transition takes place has not been answered. It has been reported that the rodent may play a role in the propagation of the fungi and that the latter are a possible reservoir of infection (2c).

The studies here presented indicate that spherules or endospores when exposed out of doors under varied conditions may go through a vegetative phase in relation to the soil, but it has also been shown that the parasitic phase may remain viable for long periods of time. A previous study in this series (1) has shown that spherule-containing exudates of humans or animals when instilled into the tracheae of guinea pigs produce isolated pulmonary lesions similar to those found in human infection. It was also shown that spherule-containing exudates kept in the icebox for as long as 110 days failed to produce hyphae or chlamydospores, but were still able to produce pulmonary infection when instilled into the tracheae of guinea pigs (1).

From the studies thus far, it may be stated that both the vegetative and the parasitic phases of *Coccidioides immitis* are infective to animals if the spores are introduced into the respiratory tract. The present study strongly suggests that both the vegetative and the parasitic phases may exist in the soil and remain viable and infective. Unfortunately, the majority of the sputum specimens (38 of 52) were from one patient who was rapidly recovering from the disease. Only 12.5 per cent of all the samples on direct culture were positive, although 55 per cent contained spherules. This fact may have influenced the survival and infectivity of the fungus, and may account for the low percentage of positive cultures and low infectivity of the older specimens injected into guinea pigs.

The detection of spherules with increasing regularity in the 30-day-old and older samples may mean a maturing of endospores not seen in younger specimens. Although the spherules seen appeared to be plasmolyzed in the majority of cases, the fact that they were not noted in some of the earlier samples indicates growth and, thus, viability. Similar bodies were seen in 158-day-old sputum aliquots kept in the icebox (12°C.) or incubator (30°C.). As with the out-of-door samples, there were periods during which spherules were not observed. These findings, as well as a similar incidence of spherules in out-of-door samples with or without earth, speak against the possibility of soil contamination.

There are criticisms which can be made concerning certain phases of the experiment. The use of X-ray film may very well exclude rays which may be deleterious to the fungus, but this feature is unavoidable because of the highly infective nature of this disease. The failure to grow the spherules after 30 days, except in one instance, is a serious criticism and casts doubt on the viability of the spherule. As has already been stated, only 12.5 per cent of 80 original samples gave positive cultures in proved cases of coccidioidomycosis. It is hoped that in future work sputum from persons infected with progressive pulmonary disease, where the viability of the spherule is greater, will be used. The increase in the percentage of specimens that had spherules after 30 days speaks for viability and is probably the result of maturing endospores which are so difficult to see on direct mount. It may be mentioned that the endospores are approximately the same size as, or perhaps a little larger than, the chlamydospores and theoretically should be as easily "wafted by the breezes" as the chlamydospores (2b). The production of definite granuloma in animals inoculated with sputum 15 days old and older speaks for a viable fungus. Here again criticism may arise out of the fact that only "ghosts" of spherules were seen on microscopic section, except in one instance. It might be argued that these lesions were produced by dead spherules in that the cultures of the lungs of such animals were consistently negative. In a previous study (2) it was shown that spherule-containing sputum inoculated intratracheally in guinea pigs produced granuloma in these animals but failed to show spherules on microscopic section of the lung. Cultures of these lesions were also negative.

Unfortunately, because of the lack of technical help it was impossible to do serial sections of the lungs. It is well known that small lesions even when seen grossly are often missed on microscopic section unless the entire block is sectioned. It is recommended that when such studies are repeated one entire lung be cultured and the other lung be serially sectioned.

## SUMMARY

1. Preliminary studies indicate that the vegetative form of *Coccidioides immitis* develops out of doors, especially in earth exposed to the sun and in the shade without soil.

2. Spherules were seen most frequently in sputum samples kept in the shade without earth, and least frequently in the sun with earth.

3. The out-of-door condition in which both phases of the fungus were seen most frequently was in the shade without earth.

4. The fungus was seen least frequently of all in specimens exposed in the sun without earth.

5. The vegetative form was rarely seen after 30 days, but the parasitic or spherule phase was evident up to 240 days of exposure.

6. The viability of the spherules was of very low order under the conditions of this experiment.

SUMARIO

*Estudios de la Contagiosidad de la Coccidioidomicosis. II. El Destino de las Esférulas en los Esputos Expuestos al Aire Libre*

1. Estos estudios preliminares indican que la forma vegetativa del *Coccidioides immitis* se desarrolla al aire libre, y en particular en la tierra expuesta al sol o en la sombra sin suelo.

2. Las esférulas fueron observadas más frecuentemente en los ejemplares de esputo mantenidos a la sombra sin tierra y menos frecuentemente al sol con tierra.

3. La situación al aire libre en que se observaron más frecuentemente ambas fases del hongo fué a la sombra sin tierra.

4. El hongo fué observado menos frecuentemente de todo en los ejemplares expuestos al sol sin tierra.

5. La forma vegetativa fué rara vez observada al pasar 30 días, pero la parásitaria, o sea la esférula, era visible hasta a los 240 días de exposición.

6. La viabilidad de las esférulas fué muy baja en las condiciones de este experimento.

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# STUDIES ON THE CONTAGIOUSNESS OF COCCIDIOIDOMYCOSIS[1]

## III. Infection in Guinea Pigs by Contact with Diseased Animals

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### INTRODUCTION

Experimental evidence regarding the contagiousness of coccidioidomycosis is meager (1). In none of the studies reported has a pulmonary lesion been produced in animals under conditions which would correspond to the conditions as they exist in humans. Analysis of the reported clinical evidence yields equivocal results. Nevertheless, most authors favor the theory of the noncontagiousness of coccidioidomycosis.

The studies here presented in guinea pigs are preliminary, and aim to reproduce the conditions which exist in humans. It is generally believed that in humans the disease is initiated in the respiratory tract in the vast majority of instances (2). A focal lesion is set up in the lung which is accompanied by a hilus lymph node complex, much the same as described for tuberculosis. As a rule, the coccidioidomycotic lesion regresses, but in a certain percentage of cases the disease progresses with the development of one or more cavities. Spherules may be isolated from the sputum in all phases of the active disease, but especially when the cavities are present. In the present study, guinea pigs were infected intratracheally with spherule-containing sputum or pus to produce pulmonary lesions simulating the human infection. The infected animals were then housed with normal animals. Cross-infection was determined by skin-testing with coccidioidin and by postmortem search for specific lesions and spherules.

### METHOD

All guinea pigs were tested initially with 0.2 ml. of coccidioidin (1:10) and O.T. (1:5) made from BCG. Six animals were instilled intratracheally by a method previously described with 0.2 ml. of sputum containing 50 spherules per ml. (actual count in Neubauer chamber). Three of the infected animals were placed in one cage with 3 controls (cages I and II). The cages were approximately 2½ by 2½ by 4 feet. The bottoms of the cages were covered by a wire mesh of one-half inch squares so that feces fell through easily into a metal pan. Caution was exercised to have these pans cleaned frequently. No perishable food was left in the cages over night.

Two other animals were instilled intratracheally with spherule-containing pus from the hilus lymph nodes of the guinea pigs that had received spherule-containing sputum intratracheally. These animals were placed in a cage for one week by themselves, and then each pig was placed in a separate cage with 4 normal animals (cages III and IV).

Animals were skin-tested every three weeks with 0.1 cc. of concentrated coccidioidin. Upon death of the animal or after periods of up to 175 days, the animals were killed and autopsied. Direct mounts in 10 per cent NaOH in 5 per cent glycerin were made of suspicious lesions in the lung or hilus lymph nodes and viewed after one hour or more of di-

[1] From the Institution for Tuberculosis Research, University of Illinois College of Medicine, Research Foundation, and the Bruns General Hospital.

gestion. Cultures on 3 per cent tryptose agar were made of similar areas. Blocks of suspicious lesions were sectioned and studied microscopically after staining with hematoxylin and eosin. Serial sections were not done.

## RESULTS

*Cages with sputum-infected animals (Nos. I and II)*: In table 1 may be seen the results in animals that lived more than three weeks. Considered by cages, the following are the pertinent findings. The animals that were instilled with spherule-containing sputum developed positive skin reactions to concentrated coccidioidin after 56 days. The control animals in cage I all gave weakly positive reactions at the same time. In cage II, 2 of the 3 control animals gave such reactions. On autopsy, the sputum-instilled animals presented minimum lesions in the lungs (figure 1) but extensive pathology in the hilus lymph nodes. In the lungs were small depressed indurated areas 3.0 to 4.0 mm. in diameter in one or both apices, while the hilus lymph nodes were usually greatly enlarged, sometimes up to 3.0 cm. in diameter. The latter contained a thick yellow pus on sectioning from which spherules in 2 of 4 animals were noted on direct mountings in sodium hydroxide. The autopsies on the control animals in cage I, as well as the cultures, were negative. In one animal of cage II, whose coccidioidin test was positive, small translucent gray indurated nodules of 1.0 to 2.0 mm. in diameter were present in both apices as well as in the other lobes. On direct mount, spherules and endospores were seen. On histologic examination focal areas of interstitial pneumonic as well as granulomatous foci were seen (figure 2). In the latter, giant cells were present, but no spherules were seen. All of the animals in cage II lost weight and died.

In summary, 5 of 6 control animals gave weakly positive coccidioidin skin tests after 56 to 125 days of contact. One of 5 animals presented lesions in the lung which were interpreted as coccidioidomycotic in character and presented spherules and endospores on direct mount, but the cultures were negative.

*Cages with pus-infected animals (Nos. III and IV)*: In cages III and IV the pus-instilled animals gave positive skin tests in 22 to 41 days following infection. In the control animals, 3 of 7 gave weakly positive reactions after 41 to 51 days of contact. On autopsy, the pus-instilled animals showed extensive pathologic changes in the lung. The lesions were pneumonic in character (involving a good portion of one or more lobes), were firm and pearly gray, and on section small pin-point, softened areas of yellow were scattered throughout. The lymph nodes were enlarged up to 1.5 cm. in diameter, were firm and diffusely gray on section. There were no lesions outside of the thoracic cage. Spherules were recovered by direct mounts and on cultures from the lungs of these animals.

In cage III, 2 of the 4 contacts lost weight and died. Two animals presented on autopsy 1.0 to 2.0 mm. reddish-gray lesions in the lung from which a rare spherule and endospore were seen in only one on direct mount. The histology in both was not typical (figures 3a and 3b).

In cage IV, one animal presented small translucent nodules 2.0 to 3.0 mm. in diameter in two lobes. The hilus lymph node was enlarged up to 6.0 mm. in

**TABLE 1**

*The Results of Housing Pulmonary Coccidioidomycotic Guinea Pigs with Normal Guinea Pigs*

| NUMBER | MATERIAL | TOTAL DAYS CONTACT | DAYS | DILUTION COCCIDIOIDIN | RESULTS IN MM. | GROSS PATH. LUNG | ORGAN EXAMINED | SPHERULES IN NaOH | CULTURE | HISTOLOGY PATH. | HISTOLOGY SPHER. | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cage I | | | | | | | | | | | | |
| A | Sputum | — | 23 to 42 | Con. | Neg. | Focal area, | Lung, | − | − | + | − | D |
| | | | 56 | Con. | 15 by 15‡‡ [A] | 1 lobe | L.N. | + | − | 0 | 0 | D |
| B | Sputum | — | 23 to 42 | Con. | Neg. | Nodule, | Lung, | + | − | + | − | D |
| | | | 56 | Con. | 15 by 15‡ | 1 lobe | L.N. | + | − | 0 | 0 | |
| $C_A$ | None | 76 | 23 to 42 | Con. | Neg. | Neg. | Lung | − | − | 0 | 0 | D |
| | | | 56 | Con. | 5 by 5‡ | | | | | | | |
| $C_B$ | None | 76 | 23 to 42 | Con. | Neg. | Neg. | Lung | − | − | − | − | D |
| | | | 56 | Con. | 8 by 8‡ | | | | | | | |
| $C_C$ | None | 71 | 23 to 42 | Con. | Neg. | Neg. | Lung | − | − | − | − | D |
| | | | 56 | Con. | 8 by $8^{\circ}_{+}$ | | | | | | | |
| Cage II | | | | | | | | | | | | |
| E | Sputum | — | 23 to 42 | Con. | Neg. | — | 0 | 0 | 0 | 0 | 0 | D |
| | | | 56 | Con. | 10 by 15‡‡ | | | | | | | |
| F | Sputum | — | 23 to 42 | Con. | Neg. | Nodules, | Lung, | − | − | + | + | D |
| | | | 56 | Con. | 20 by 20‡‡ | 1 lobe | L.N. | − | − | | | |
| $C_D$ | None | 76 | 23 to 42 | Con. | Neg. | Neg. | Lung | − | − | − | − | D |
| | | | 56 | Con. | Neg. | | | | | | | |
| $C_E$ | None | 175 | 23 to 42 | Con. | Neg. | Nodules, | Lung, | +• | − | + | − | D |
| | | | 56 | Con. | Neg. | 4 lobes | L.N. | − | − | 0 | 0 | |
| | | | 125 | Con. | 5 by 5‡ | | | | | | | |
| $C_F$ | None | 104 | 23 to 42 | Con. | Neg. | — | 0 | 0 | 0 | 0 | 0 | Animal lost |
| | | | 56 | Con. | 5 by $5^{+}_{+}$ | | | | | | | |
| Cage III | | | | | | | | | | | | |
| $A_B$ | Pus | — | 22 | Con. | Neg. | All lobes | Lung | +• | + | 0 | 0 | Isolated one week |
| | | | 41 | Con. | 14 by $16^{+}_{++}$ | | | | | | | K |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_{AB}$ | None | 55 | 27 | Con. | Neg. | Focal area, | Lung | − | − | − | − | D |
| | | | 51 | Con. | 4 by $5^{0}_{+}$ | 1 lobe | | | | | | |
| $C_{B2}$ | None | 62 | 13 | Con. | Neg. | Both apices | Lung | +* | − | + | − | K |
| | | | 44 | Con. | Neg. | | | | | − | | |
| $C_{C2}$ | None | 82 | 21 | Con. | Neg. | Neg. | Lung | − | − | 0 | 0 | K |
| | | | 41 | Con. | Neg. | | | | | | | |
| | | | 63 | Con. | Neg. | | | | | | | |
| $C_{D2}$ | None | 46 | 21 | Con. | Neg. | Neg. | Lung | − | − | 0 | 0 | D |
| | | | 41 | Con. | Neg. | | | | | | | |
| Cage IV | | | | | | | | | | | | |
| $B_A$ | Pus | — | 22 | Con. | 10 by $12^{\ddagger\ddagger}$ | 4 lobes | Lung | +* | + | 0 | 0 | K |
| | | | 42 | Con. | 12 by $12^{\ddagger\ddagger}$ | | | | | | | |
| | | | 65 | | 15 by $15^{\ddagger\ddagger}$ | | | | | | | |
| $C_{E2}$ | None | 82 | 22 | Con. | Neg. | Neg. | Lung, | + | − | 0 | 0 | K |
| | | | 41 | Con. | 4 by $6^{0}_{+}$ | | L.N. | − | − | | | |
| $C_{F2}$ | None | 82 | 22 | Con. | Neg. | Nodules, | Lung, | + | − | + | 0 | K |
| | | | 41 | Con. | Neg. | 2 lobes | L.N. | − | − | | | |
| | | | 65 | Con. | Neg. | | | | | | | |
| $C_G$ | None | 66 | 26 | Con. | 10 by $12^{++}_{0}$ | Neg. | Lung, | − | − | 0 | 0 | K |
| | | | 49 | Con. | 3 by $4^{+}_{-}$ | | L.N. | − | − | | | |

Con. = Concentrated.
* Endospores also.
+ Positive.
− Negative (also NEG.)
0 = Not done.
D = Died.
K = Killed.
△ upper (+) = Redness.
lower (+) = Induration.

diameter, gray and firm. The spleen was enlarged. On direct mount made of the lung lesions, a few spherules were seen (figure 4). The histology of the lung was

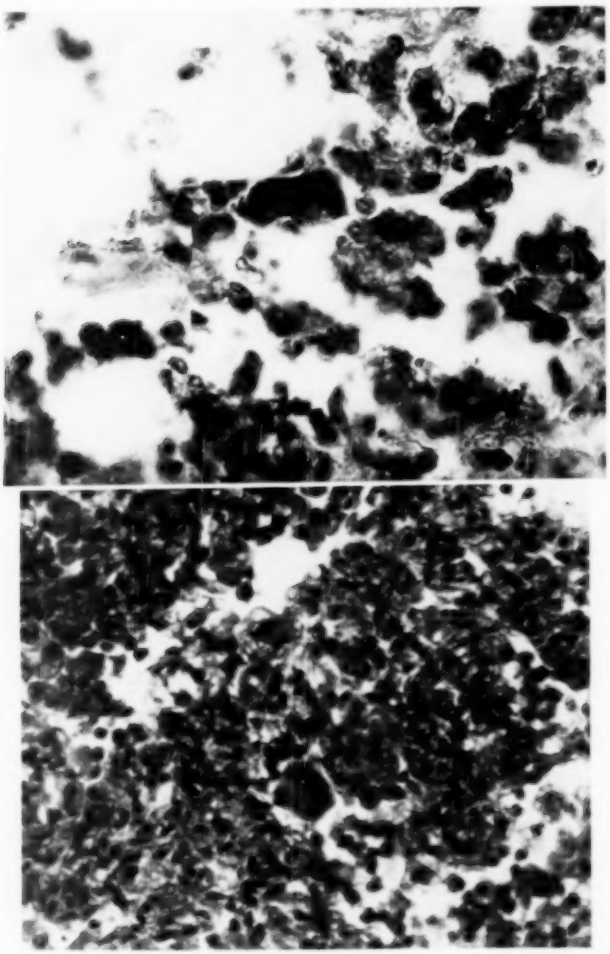

FIG. 1. (Upper) Guinea pig F (cage II). Intratracheal instillation of sputum. Granuloma of lung showing giant cell and swollen histiocytes.

FIG. 2. (Lower) Guinea pig CE (cage II). Contact 175 days. Granuloma with giant cell of lung. Spherules seen on direct mount and plasmolyzed spherules noted in section.

typical, but no spherules were noted (figure 5). In another animal in which no gross pathologic changes were noted in the lung, spherules were recovered (figure 6).

In summary, 3 of 7 animals gave weakly positive skin tests after 41 to 51 days of contact. Three of the 7 presented spherules in direct mounts of the lung. Only one of the 3 animals with lung lesions presented typical granuloma histology.

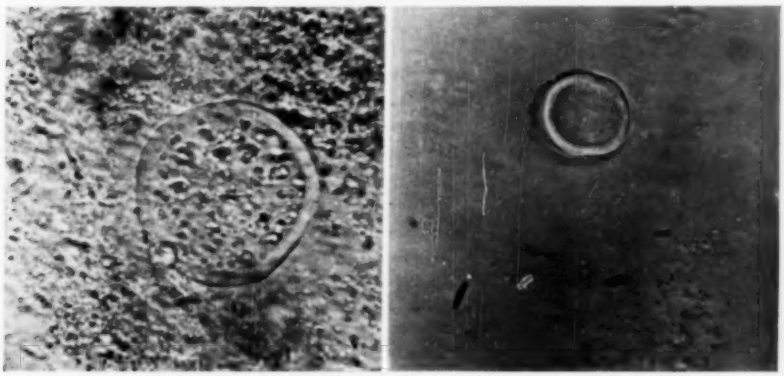

FIG. 3a (Left) and 3b (Right) Guinea pig $C_{82}$ (cage III). Various types of spherules seen on direct mount from lung. Same magnification showing difference in sizes. (Contact 62 days)

FIG. 4. Guinea pig $C_{72}$ (cage IV). Direct mount from lung showing plasmolyzed spherule.

*Summary of All Contact Studies*

Of 13 control animals exposed from 46 to 175 days to guinea pigs that were infected intratracheally with spherule-containing exudates which produced intra-

pulmonary lesions, 10 of the contacts presented either a weak positive skin test, pathologic changes in the lungs, or spherules on direct mount of the lesions.

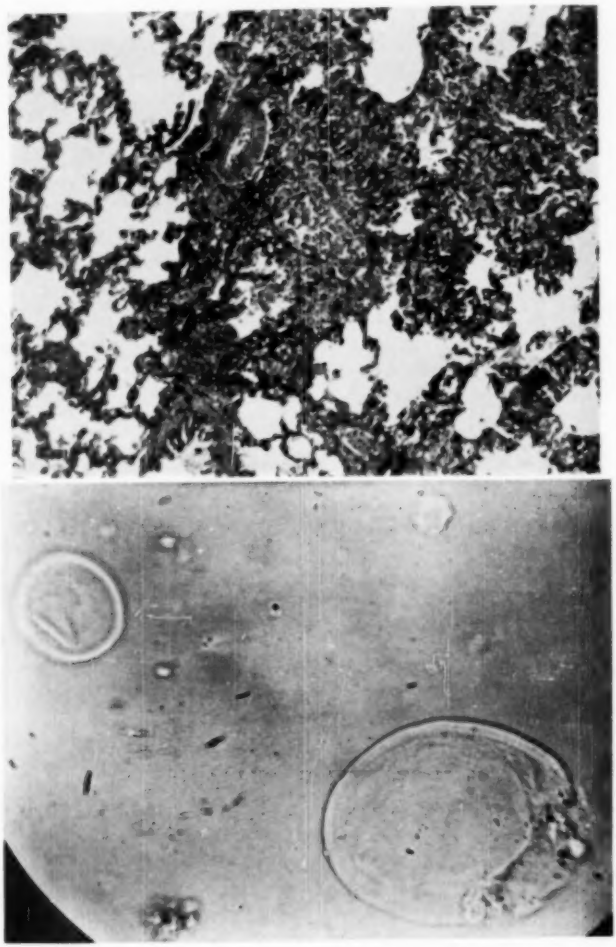

FIG. 5. (Upper) Guinea pig $C_{F2}$ (cage IV). Focal granuloma of lung with central giant cell. (Contact 82 days)

FIG. 6. (Lower) Guinea pig $C_{E2}$ (cage IV). Plasmolyzed spherules of various sizes from lung where no gross pathology was noted. (Contact 66 days)

Cultures of the lung and hilus lymph nodes of the control animals with suspicious lesions were all negative, as were those of the sputum-instilled animals. The pus-instilled animals yielded positive cultures.

## DISCUSSION

The findings here presented are to be considered of a preliminary nature. Unfortunately, with the closing of the Bruns General Hospital where the experiment was conducted, the work was curtailed. It is obvious that a larger group of animals should be studied, and that the diseased animals should be infected intratracheally by sputum containing more spherules or by spherule-containing pus so that larger pulmonary lesions are produced. In evaluating results, the skin reactions, direct mount studies, and the gross microscopic findings will be considered in that order.

*Skin reactions:* False reactions to coccidioidin in animals are considered rare. On the other hand, definite infection, as proved by culture, gross and microscopic studies, may fail to give a positive skin test or may give weakly positive reactions, especially shortly after infection (22 days) (3).

All animals in this study before and shortly after infection were negative to coccidioidin (1:10 or concentrated). In some of the heavily infected animals, the test did not become positive until 56 days after infection. The above data indicate that skin reactions of low order are probably significant.

In 8 of the 13 contact animals there was a weakly positive reaction as characterized by redness and induration, albeit with less than 10 mm. of induration.

*Lesions of the lung:* The typical gross lesion in experimental intratracheal infection with spherule-containing sputum or pus in guinea pigs (3) is a translucent gray, firm, indurated area in the apices of the lung or in any of the lobes. Spherules may or may not be seen on direct mounts in NaOH or by microscopic section. Usually, however, a typical granuloma with giant cells is found. As already stated, the pathologic change produced by spherule-containing pus is much more extensive in character, producing pneumonic lesions from which numerous spherules can be recovered and cultured.

Of the 13 normal animals kept in contact with the infected animals, 4 showed gross lesions of the lung. Of the 4, spherules were found in 3 on direct mounting, albeit they were few in number and mostly plasmolyzed. In one lung specimen, spherules were seen but no gross pathology was noted. On microscopic examination, 2 of the 3 presented what was considered to be typical granuloma without spherules, as produced by spherule-containing sputum. Unfortunately, because of limitation of technical help, serial sections were not done. Small lesions seen grossly were missed many times on sectioning.

*Spherules recovered on direct mount:* In 4 animals of the 13 in the contact group, spherules or endospores were seen on direct mount of minced lung suspended in sodium hydroxide. Cultures of the organs of the contact animals were uniformly negative. In a previous study (3), as well as in this one, however, instillations of spherule-containing sputum produced pathognomonic lesions in the lung which were negative on culturing.

The object of this study was to determine whether or not coccidioidomycosis is a contagious disease that could be passed from animal to animal. An attempt was made to reproduce the conditions as they exist in humans: namely, the production first of an intrapulmonary lesion in the animals, and then housing

such animals with normal ones. Previous experiments have not been set up under these conditions. For example, Jacobson (1a) infected his animals intraperitoneally and then housed them with normal animals. Smith (1b) exposed normal animals to others having draining testicular abscesses. He states that no cross-infection was noted, as was determined by skin-testing and complement fixation only.

Clinical evidence that coccidioidomycosis is not contagious is equivocal. The fact that up to 80 per cent of the permanent population of the southern San Joaquin valley of California are infected, as determined by skin-testing (4), may speak as well for the disease being contagious as for the theory that only the chlamydospores of the vegetative phase disseminated by dust can infect man (5).

Experimental evidence in the present series of studies (3, 6) has shown that: (*1*) Spherules in sputum or pus when instilled intratracheally in animals will produce typical infection (3); (*2*) Both the vegetative and the parasitic forms of the *Coccidioides immitis* are found in sputum exposed out of doors with or without earth, and both can be infective when instilled intratracheally or injected intraperitoneally into animals (6); (*3*) Guinea pigs with pulmonary lesions of coccidioidomycosis can transmit the infection to normal guinea pigs housed with them.

The sum total of these studies strongly indicates that coccidioidomycosis can be contagious, and until proved otherwise should be considered so.


## SUMMARY

1. Normal animals when housed with guinea pigs having pulmonary coccidioidomycosis may develop gross pulmonary lesions or other evidence of infection.

2. Ten of 13 normal animals housed in four separate cages with infected animals presented evidence of infection after 46 to 175 days of contact, as determined by positive skin tests, pulmonary lesions, or by spherules seen on direct mounts of these lesions.

## SUMARIO

*Estudios de la Contagiosidad de la Coccidioidomicosis. III. Infección en los Cobayos por Contacto con Animales Enfermos*

1. Cuando se albergan cobayos normales con otros que muestran la patología pulmonar de la coccidioidomicosis, los primeros pueden revelar lesiones pulmonares macroscópicas u otros signos de infección.

2. Diez de 13 animales normales albergados en cuatro jaulas distintas con animales infectados presentaron signos de infección al cabo de 46 a 175 días de contacto, según se determinó por medio de cutirreacciones positivas, lesiones pulmonares o de la observación de esférulas en los montajes directos de dichas lesiones.


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# TUBERCULOSIS OF THE STOMACH AND THE STOMACH IN TUBERCULOSIS[1]

## A Review with Particular Reference to Gross Pathology and Gastroscopic Diagnosis

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### INTRODUCTION

As in the case of so many rare diseases, tuberculosis of the stomach has received a great deal of attention from clinicians and pathologists. In spite of the fact that to the present probably no more than 400 cases with any pathologic validity at all have been reported, the subject has called for critical review from time to time: in 1917 by Broders (6); in 1931 by Good (24); in 1935 by Rodríguez Olleros and de la Viesca (43); in 1938 by Clagett and Walters (12); and in 1945 by Binder, Ruby, and Shuman (5). Many detailed case reports are to be found in the literature and extensive simple statistical information is available. Nevertheless, in less than a dozen cases has the correct diagnosis been made prior to pathologic study.

The clinical recognition of the tuberculous nature of a gastric lesion is an important matter, but of more practical clinical value is an appreciation of the physiologic and anatomic gastric peculiarities of the general run of tuberculous patients who have stomach complaints but no tuberculous stomach lesions. This less spectacular aspect of the problem has received in comparison little attention.

The subject of tuberculosis and stomach disease finds itself at present, therefore, in a rather peculiar position. There is a large amount of collected knowledge concerning its rarest manifestation but a continued difficulty in clinical recognition, and there is a rather poor understanding of its commonest less specific associations. It is with these thoughts in mind that the following review is presented.

### TUBERCULOUS LESIONS OF THE STOMACH

#### *Incidence*

Specific tuberculous lesions rarely occur in the stomach; how rarely, it is somewhat difficult to say. Different writers have shown varying inclinations to accept previously reported cases. Broders (6), whose histopathologic criteria for diagnosis were strict, accepted as positively proved only 49 of 306 cases which had been described to 1917. Chaffin (11) believed that only 5 more proved cases were added to the literature during the next twenty years, bringing the total to 54 by 1937. However, because in retrospect it is difficult, and possibly unfair, for a reviewer to attempt to judge the validity of a previously described case, most authors have felt it best merely to total the cases as they have been reported. Thus, Clagett and Walters (12) stated that 368 cases had been described to 1938,

[1] From the Gastrointestinal Section, 98th General Hospital, U. S. Army, European Command, APO 407.

without presuming to pass judgment. This appears to be a good way to think of the incidence of this particular disease if one maintains a certain skepticism regarding the possibility of diagnostic error.

Of more practical help than the total number of reported cases is the incidence of the disease as it has been found, and, therefore, as it may be expected by the clinician, among consecutive hospital admissions, resected stomachs, and autopsies (tables 1, 2, 3, 4). One case of gastric tuberculosis was found among 21,000 consecutive admissions of the general hospital type in one series (53). Thirty

TABLE 1

*Incidence of Gastric Tuberculosis by Hospital Admissions*

| REFERENCE | CLINIC | TYPE OF ADMISSIONS | PERIOD | NUMBER HOSPITAL ADMISSIONS | NUMBER CASES OF GASTRIC TUBERCULOSIS |
|---|---|---|---|---|---|
| Windwer (53) | Jewish Hospital of Brooklyn | General hospital | 1913–1944 | 21,000 | 1 |
| Browne, McHardy, and Wilen (8) | Charity Hospital of New Orleans | Tuberculosis service | 1923–1942 | 23,278 | 30 |

TABLE 2

*Incidence of Gastric Tuberculosis Found at Gastric Surgery*

| REFERENCE | NUMBER CONSECUTIVE GASTRIC OPERATIONS | NUMBER CASES OF GASTRIC TUBERCULOSIS |
|---|---|---|
| Broders (6) | 2,501* | 1 |
| Good (24) | 7,416* | 3 |
| Clairmont (13) | 258 | 2 |
| Demel (19) | 1,568 | 3 |
| Mirolli (quoted by Binder, Ruby, & Shuman (5)) | 1,134 | 1 |
| Szacsvay (quoted by Binder, Ruby, & Shuman (5)) | 345 | 1 |
| Knoflach & Pape (31) | 4,000 | 5 |
| Collinson & Stewart (15) | 320 | 3 |
| Totals | 17,542 | 19 |

* It is not clear whether Good's figures include those reported by Broders.

cases were discovered among 23,278 admissions to the tuberculosis service of another (8). During 17,542 collected stomach operations, gastric tuberculosis was discovered nineteen times (table 2). Among 96,251 unselected routine autopsies, 159 instances of the disease were found (table 3), while among 20,585 autopsies on patients whose primary disease was tuberculosis, 117 cases were uncovered (table 4). The rarity of gastric tuberculosis is apparent from these figures, and it becomes evident, of course, that the greatest obstacle to correct clinical diagnosis must be that which is contributed by clinical unfamiliarity.

### *Pathogenic Mechanisms*

Accurate diagnosis requires an understanding of the means whereby the tuberculous process becomes established in the gastric wall. On this point clinical speculation has dominated experimental study; nevertheless, there has been rather close general agreement on the matter. The facts that specific gastric lesions are rare and that specific intestinal lesions are common, so common that they have "sometimes been considered a part" (18) of chronic pulmonary tuberculosis,

TABLE 3

*Incidence of Gastric Tuberculosis Found during Routine Autopsies*

| REFERENCE | NUMBER AUTOPSIES | NUMBER CASES OF GASTRIC TUBERCULOSIS |
|---|---|---|
| Good (24) (quoting Claylor & Wilkinson, Glaubitt, Gossmann, Grusdew, Heubschmann, Ophüls, Orsòs, Robertson) | 71,871* | 153 |
| Sullivan, Francona, & Kirshbaum (47) | 11,480 | 2 |
| Collinson & Stewart (15) | 10,000 | 3 |
| Cameron (9) | 2,900 | 1 |
| Totals | 96,251 | 159 |

* Some authors have counted twice certain of the series making up this figure.

TABLE 4

*Incidence of Gastric Tuberculosis Found at Autopsy of Patients with Pulmonary Tuberculosis*

| REFERENCE | NUMBER AUTOPSIES | NUMBER CASES OF GASTRIC TUBERCULOSIS |
|---|---|---|
| Cullen (18) | 1,043 | 4 |
| Browne, McHardy, & Wilen (8) | 1,321 | 30 |
| Good (24) (quoting Eisenhardt, Glaubitt, Gossman, Kundrat, Letulle, Melchior, Ophüls, Plambeck, Simmonds) | 15,165 | 80 |
| Sullivan, Francona, & Kirshbaum (47) | 554 | 2 |
| Hardt and Cohen (27) | 1,102 | 1 |
| Crawford and Sawyer (17) | 1,400 | 0 |
| Totals | 20,585 | 117 |

have, of course, engendered considerable thought. The explanations usually (6, 24, 50, and others) offered: surface integrity of the gastric mucosa, a local immune reaction, rapid passage of ingested organisms, relative paucity of gastric lymphatic tissue, and adverse effects of gastric juice on the bacilli, are reasonable enough to invite acceptance, whether or not there may be additional, as yet undetected, mechanisms at work. Sullivan, Francona, and Kirshbaum (47) have been the main protagonists of the theory that the stomach must have "some peculiar natural immunity to the tubercle bacilli, a protection lacking altogether in the intestinal tract." In support of a probable protective mechanism afforded

by the paucity of gastric lymphoid tissue, it has been pointed out (35) that most cases of gastric tuberculosis are found in the prepyloric region where the lymphatic supply is relatively most abundant, but it is thought that this point does not offer convincing evidence. It must be noted too that, if gastric juice plays a protective role, it must affect the invasive powers rather than the mere viability of the tubercle bacillus, for gastric juice has no demonstrable effect on the organism for many hours *in vitro* (8 and others). Furthermore, in considering the protective mechanism of rapid gastric emptying, it must be borne in mind that this is obviously a protection of secondary importance, because flow through the often affected small bowel is more rapid.

The possible routes taken by the tubercle bacillus in reaching the stomach have been listed as four by Broders (6) and accepted in a general way by most authors. Passage by blood dissemination is usual. Browne, McHardy, and Wilen (8) have briefly proved the mechanism experimentally, and several authors, notably Nicolò (36), have felt that they have observed clinical evidence of the process. In generalized miliary tuberculosis the stomach may be involved. Because in miliary tuberculosis, as well as in other forms of gastric tuberculosis, the lesions tend to predominate in the submucosa, Froehlich (23) felt that the fundamental importance of the embolic nature of the process could not be doubted. Direct extension of infection to the gastric wall from neighboring organs, particularly from caseating lymph nodes, has been found clinically but appears to be an uncommon pathogenic mechanism. The extension of a tuberculous process in a retrograde fashion along the gastric lymphatics seems possible, but there is little available information on this point.

The possibility that the gastric wall may become infected by direct contact of tubercle bacilli with the mucosa has been given serious consideration, particularly because it has been shown that intestinal tuberculosis is most frequent in those patients with the largest numbers of bacilli in their sputum (7, 18). There has been a gradual crystallization of opinion, however, about the belief that in reality the possibility of direct infection of the stomach is very remote. In 1917, Broders (6) found that primary tuberculosis of the stomach had been claimed in 4 cases, but in 1931 Good (24) felt that there had never been an acceptable case. Broders had stated that it was "... safe to say that infection of the normal mucosa of the stomach is difficult. However, it seems reasonable to conclude that a lesion associated with reduced acidity renders such infection easier." Nevertheless, Froehlich (23) pointed out that experimentally it had never been possible to produce gastric lesions by feeding masses of bacilli; and Browne, McHardy, and Wilen (8) were not able to produce specific changes by applying cultured bacilli of unquestioned virulence directly to the traumatized mucosa of canine gastric pouches.

### *Distribution of Tuberculous Lesions in the Stomach*

Although there is no well-defined site of predilection for specific tuberculous lesions within the stomach (table 5), in most cases they occur in the antrum and along the lesser curvature of the pars media. This fact, if moderated by the realization that no part is immune, is of some help in clinical diagnosis. Walters,

Kirklin, and Clagett (50) found that tuberculous ulcers, particularly, are found in the pylorus and lesser curvature, and Connolly (16) came to the same conclusion. Hartz and van der Sar (29) pointed out that the cardiac region is relatively immune, but Broders (6) and Binder, Ruby, and Shuman (5) were able to collect 15 cases from the region.

### *Classification of Gross Pathologic Types*

Of the several classifications of the gross manifestations which have been offered (1, 4, 5, 6, 8, 24, 32, 41), that published by Biernath in 1921 (4) is most helpful for diagnostic purposes. It is important to note that the stomach affected with tuberculosis may demonstrate several types of gross lesions. Biernath (4) believed that, in addition to a nonspecific simple gastritis, tuberculosis may manifest itself in the stomach by (a) multiple small mucosal erosions; (b) ulcers; (c)

TABLE 5

*Distribution of Tuberculous Lesions in the Stomach, as Reported*
There is some duplication of figures in the three series

| | BRODERS (6) | BINDER, RUBY, & SHUMAN (5) | GOOD (24) | TOTAL* |
|---|---|---|---|---|
| Number of cases | 55 | 40 | 26 | 121 |
| Cardia | 4 | 11 | | 15 |
| Lesser curvature | 13 | | 9 | 22 |
| Greater curvature | 8 | | 2 | 10 |
| Anterior wall | 1 | | 4 | 5 |
| Posterior wall | 6 | | 7 | 13 |
| Pars media | | 21 | | 21 |
| Antrum | | 19 | | 19 |
| Pylorus | 16 | | 17 | 33 |
| Generalized | 7 | 3 | | 10 |

* Note that the authors have classified the anatomic locations in different fashions; Binder, Ruby, and Shuman have merely divided the stomach into its three lineal sections. The last column must be interpreted accordingly.

an infiltrating tumorous ("hypertrophic") form; (d) a sclerosing inflammatory form; (e) an acute miliary dissemination; and (f) pyloric obstruction, either by extragastric compression, by extension from peripyloric nodes, or by invasion from other neighboring organs.

*Secondary gross deformities of the stomach:* The gross distortions of gastric configuration produced by the lesions are those which accompany tumor formation and cicatricial contraction. Such changes occur most frequently in the antrum and are most often reflected by pyloric stenosis. Watson, Flint, and Stewart (51) in 1936 reported a case in which a pars media lesion produced an hourglass deformity.

*The ulcer type:* Gross tuberculous lesions of the stomach usually assume an ulcerous form. Of the cases reviewed by Binder, Ruby, and Shuman (5), 95 per

cent showed ulcers, and these writers went as far as to conclude, "The other types occur so infrequently that they are of little practical significance." Walters, Kirklin, and Clagett (50) found that 80 per cent of the lesions are ulcers, while Browne, McHardy, and Wilen (8) placed the figure at 57 per cent. Most of the ulcers occur at the distal end of the lesser curvature, with a tendency to extend over to the posterior wall (24). The case of Sullivan, Francona, and Kirshbaum (47) was rather unusual in this connection, for at autopsy it was found that there were several geographic ulcers two to five centimeters in diameter confined to the cardia and fundus.

It is believed that the ulcer always develops as a result of fistula formation from a submucosal focus. Small submucosal emboli grow as tubercles and with eventual caseation and suppuration they produce multiple fistulas through the mucosa into the gastric lumen. Ulcers then develop by numerous irregular ruptures of the mucosa, which are responsible for the serpiginous outline of the chronic ulcer. Submiliary nodules surround the ulcer and eventually caseate and break down to cause further expansion. Because of the fistulization process, the ulcers are most often multiple (23, 37). The muscularis propria is infrequently involved (50) and, although autopsy demonstration of an ulcer's extension to the serosa has been recorded (47), and although free perforation is not unknown, shallowness is the rule. "Perforation seemingly is its least characteristic feature" (24). Eventually cicatricial contraction distorts the area, with the production of heavy scarring and adhesion to neighboring organs. Then deep centrifugal fistulization may proceed, with development of extensive excavated tracts, often enlarging into abscesses at their termini (37).

It is apparent from the pathogenesis that the tuberculous ulcer must have a larger submucosal diameter than surface diameter and that the undermined edges must typically be ragged, edematous, and grossly inflamed. Discrete tubercles are often present at the edges, eventually to play their part in the propagation of the destructive process. The growth and denudation probably can go on indefinitely until the patient succumbs. Broders (6) stated that an ulcer diameter of 20 by 10 centimeters may be realized. The granulomatous base of the ulcer is characteristically a dirty gray-brown and it is itself at times covered with easily discernible tubercles. Clagett and Walters (12) believed that multiple small mucosal erosions and ulcers constitute one of the rarest types of lesion. In Hamilton's case (26), however, 115 to 120 small erosions were found involving most of the mucosa.

The gross anatomy of the tuberculous ulcer is best studied gastroscopically, for only by this method can the lesion be observed in its living state. There is great diagnostic advantage in being able to study the living colors contributed by an active blood flow and in being able to spread the tissues with their lesion by insufflating the intact living stomach. Gastroscopic studies, unfortunately, have been few.

The case of ulcerous gastric tuberculosis of Gutzeit and Teitge (25), published in 1937, was particularly well described and illustrated. In this instance, gastroscopy revealed diffuse atrophic gastritis, with submucosal vessels visible over an

extensive area. The mucosa was thin and in places spotted with red. In the region of the antrum, on and distal to a fold stretching across the greater curvature from one wall to the other, six ulcers were present. The ulcers were elongated, ran obliquely across the axis of the stomach, and were 0.5 cm. deep, with pale sharp edges and rough gray-yellow bases. The resected specimen proved the accuracy of the preoperative observations, and the histologic study revealed tuberculosis.

In 1945, Howard (30) described the gastroscopic picture of a lesion which may be considered more typical. There were "... multiple ulcerations ... some of the ulcers were shallow and some were deep; all were serpiginous in outline and all had dirty gray bases." It is unfortunate that so little information about the patient was supplied.

Moersch's case (34), described in 1943, is of particular interest because here the lesion involved the tissues on both sides of a gastroenterostomy stoma. In a patient who had had a partial gastrectomy, gastroscopy revealed a lesion which closely simulated a simple gastrojejunal ulcer. In the base of the ulcer, however, there were numerous small nodular elevations, and other tubercles were present under both the jejunal and the adjacent gastric mucosa.

The review of the gross stomach findings in a few cases of tuberculous ulcer is helpful for pointing out the typical character of the lesion as it is seen at autopsy and at surgery.

Connolly (16) reported the case of a 45-year-old female with a mass in epigastrium At autopsy five ulcers from one-eighth to three-fourths of an inch in diameter were found in the mid-portion of the lesser curvature. Their outlines were irregular and their edges undermined. There were two small nonulcerated caseous masses lying intramurally near the pylorus. Acid-fast organisms were demonstrable in the stained tissue sections and it was seen that the serosa formed the floor of the ulcers.

Hartz and van der Sar (29) described the case of a 59-year-old Negro male whose stomach was found to be contracted on post-mortem examination. On the lesser curvature 3 cm. distal to the cardia there were two ulcers, 2 cm. apart, measuring 4 by 10 and 6 by 10 mm. The long axis of one paralleled the curvature, and that of the other ran obliquely across it. The ulcer edges were deeply undermined, and this process had been extensive enough to connect the two lesions submucosally, even though the craters were 2 cm. apart.

Chaffin (11) described a resected specimen which contained an indurated area 4.5 cm. in diameter on the serosal surface, with many nodules and a mural thickness of 1.5 cm. Corresponding to this lesion there was on the mucosal surface a very shallow ulcer which, upon histologic examination, was found to extend no deeper than the muscularis mucosae.

Nicolò (36) described the roentgenographic examination of a 52-year-old white male who had already had a gastroenterostomy which revealed a gastric lesion 6 to 7 cm. distal to the cardia. After resection, an ulcerocicatricial type of lesion was found, characterized by ulceration which involved a great loss of substance, plus intense proliferation reaction in the serosa.

*The infiltrative or hypertrophic type:* The infiltrative or hypertrophic type is not rare among reported cases and, in fact, Logeais (32) considered it the most common assumed by gastric tuberculosis. On the other hand, Binder, Ruby, and Shuman (5) considered only one of their 40 reviewed autopsy cases to fall within this category. The reason for such discrepancy is found in the fact that any single tuberculous lesion in the stomach may present several gross characteristics

and that its classification in certain cases is a rather arbitrary matter. Thus, the lesion which is predominantly hypertrophic is often ulcerated as well. It must be emphasized at this point that the tuberculous gastric lesion is one lesion and that it is categorized into different gross types, according to its individual peculiarities, merely for diagnostic and pathologic convenience.

The hypertrophic type is characterized by submucosal infiltration, which is usually (12, 23, 40) localized at the antrum. An annular indurated thickening of the gastric wall is produced. The infiltration may spread through the entire stomach, eventuating in a linitis plastica; in Pohl's case (38), the gastric wall was infiltrated from cardia to pylorus. There may be a great overproduction of granulation tissue, but this excess is spread diffusely through the involved region, thus differentiating the lesion from the tumor type. Subsequent cicatrization with gastric obstruction is a common sequel. The mucosa itself usually remains intact during the early life of the lesion and, because its usual location in the pyloric region encourages early clinical recognition, resection is frequently done prior to progression to caseation and ulceration. Renander (41) and Froehlich (23) stated that the surface often shows superficial erosions, but it is likely that these represent the nonspecific mucosal erosions which are so often secondary to gastric retention of any etiology. There is, however, one important mucosal change contributed by submucosal granulomatous infiltration. As a consequence of the mass of the lesions and by mechanical interference with the action of the muscularis mucosae, the gastric rugae are obliterated and the mucosa is converted to a flat surface or is thrown into large irregular frozen folds.

A few cases are reviewed because they demonstrate points of interest:

Froehlich (23) reported the case of a 45-year-old man who had a four-month history of vomiting. Roentgenographic examination showed a large crater in the antrum plus a stenotic lesion at the pylorus. Upon resection, no ulcer was found. Rather, the mucosa was intact, but there was a triangular absence of submucosal substance over an area measuring 1.5 by 1.0 cm., with dense typical tuberculous submucosal granulation surrounding the depression and heavily infiltrating the prepyloric region.

Windwer (53) reported the case of a 35-year-old female with roentgenographic findings suggestive of an antral polyp. At operation there was great thickening at the pylorus and the stomach was markedly dilated. The operative diagnosis was inoperable carcinoma, but examination of material obtained by biopsy revealed tuberculosis.

Logeais (32) reported the case of a 35-year-old woman with the clinical and roentgenographic picture of pyloric stenosis plus an orange-sized para-umbilical tumor. The resected specimen showed enormous hypertrophy at the pylorus, with the formation of a smooth rigid cylinder. In cross section the gastric wall measured 5 cm. Proximal to the thickening there were two small ulcers with irregular violaceous edges.

Morris (35) reported the case of a 23-year-old Negro male who presented the characteristic findings of intestinal obstruction. On resection the stomach was found to be greatly dilated and there was a large irregular mass at the pylorus. The antral wall was tremendously thickened, and it was found that this was largely due to submucosal infiltration. Several pyloric erosions were present.

In Renander's case (41), roentgenographic examination of a 48-year-old female demonstrated a "clumsy" infiltrated gastric wall but normal peristalsis. A small stomach with no palpable disease was found at operation. The resected specimen grossly appeared normal but histologically there was marked tuberculous infiltration of the submucosa and muscularis propria.

*The tumor type:* It has been thought permissible to delineate a tumor form from the hypertrophic. Both are characterized by proliferation, but in the tumor type the overgrowth is to some extent circumscribed. Its gross characteristic is the rather discrete nature of the mass. As opposed to the more diffuse type, the tumor variety tends to caseate early, with liquefaction, fistulization, and ulceration. Intramural tuberculous abscesses of this type apparently are prone to secondary infection, the result being a subacute phlegmonous gastritis. Needless to say, however, little is known about the complications of such a rare disease. Again, the pyloric region is the favorite site (24).

Sullivan, Francona, and Kirshbaum (47) have furnished two good examples of the tumor type. In one patient a caseous nodule 16 mm. in diameter and 6 mm. high was found intramurally. The other demonstrated several caseated tumors, pin-head to split-pea in size, scattered along the lesser curvature.

*The inflammatory type:* There is no justification for this category in a classification based on gross characteristics, but it must be delineated because there is some suspicion that this type may be responsible for secondary superficial adenomatous proliferation and true mucosal polyp formation in the tuberculous stomach (41). The tissue changes are said to be due to a toxic influence (41). The following two cases may fall within the group:

Good (24) reported the case of a 40-year-old male who had a palpable epigastric mass, with roentgenographic findings of a small ulcer on the lesser curvature. At operation a large ulcerated infiltration was found. Histologically, there was an inflammatory lesion, with typical tubercles and a tremendous lymphocytic cellular reaction.

Renander (41) reported the case of a 67-year-old woman who was found to have a smooth filling defect on the lesser antral curvature when examined roentgenologically. At operation a well-limited tumor could be palpated. A broad-based polyp was found in the resected specimen. Histologically it was demonstrated that the base of the adenoma was ringed by a characteristic tuberculous tissue reaction but that the polyp itself contained no specific tissue changes.

*Gastric tuberculosis and carcinoma:* The coexistence of gastric tuberculosis and gastric carcinoma is notably common, as compared with coexistent tuberculosis and malignancy elsewhere in the body. In 1943 White (52) stated that 10 per cent of the reported cases of gastric tuberculosis had been complicated by gastric carcinoma.

In 1938 Clagett and Walters (12) stated:

This incidence of association is rather high, certainly higher than occurs in most organs of the body in which these conditions can coexist. Perhaps this can be accepted as evidence in support of the theory that cancer, ulcer and erosion of the gastric mucosa may lower its resistance to tuberculous infection and act as portals of entry for infection. Certainly, this incidence of associated lesions seems too high to be explained entirely by coincidence.

In 1943 MacCarty (33) countered with an opinion which has not received general acceptance:

In a series of more than 3000 gastric carcinomas I have seen an associated gastric tuberculosis twice. This association is probably no greater than the combination in other por-

tions of the body. I am inclined to believe that tuberculosis is not a predisposing factor in gastric carcinoma. As a matter of fact, carcinomatous patients rarely have an active tuberculosis.

The possible causal relationships between the two diseases pose a problem of considerable proportions, reaching a sort of climax in White's case (52) of coexistent pernicious anemia, gastric cancer, and gastric tuberculosis. The interrelationships are complicated, involving among other factors the possible effects of achlorhydria on the tubercle bacillus, tuberculous tissue reaction as a possible pre-malignant irritative factor, and malignant tissue disruption as a portal for tuberculous invasion. Sprunt (46) felt that the tuberculosis in his case of simultaneous involvement had reached the stomach by direct extension from the peritoneum. He pointed out that coexistence of the two diseases would be very common if the achlorhydria and gastric retention of carcinoma played an important role in the genesis of gastric tuberculosis.

Sprunt's case (46) was rather typical of the condition:

A 70-year-old man was operated upon for an acute illness and a perforated gastric lesion was closed. He died twenty-three days later, and at autopsy a mass 10 cm. long and 1 to 2 cm. thick was found extending proximally from the pylorus and almost encircling the stomach. The mucosal surface showed a heaping up at the edges of the tumor and a depression in the center. In the middle of the mass there was a perforation. An unassociated benign pedunculated adenoma 2.0 by 2.5 cm. emerged at the cardia. Acid-fast bacilli were found on stained section of the tuberculous granulations which were interspersed among the carcinomatous tissue.

*Gastric tuberculosis and sarcoma:* A case of associated tuberculosis and lymphosarcoma in the stomach was reported by Rentschler and Travis (42) in 1934:

A 65-year-old female with a twenty-two-year history of gastric complaints was found on roentgenographic examination to have a large filling defect involving both curvatures at the middle third of the stomach. There was 85 per cent gastric retention at five hours. At operation the stomach was small. The wall was firm, with irregular masses involving the whole organ except the fundus. There was ulceration, plus a segment of stenosis. On microscopic examination, lymphosarcoma and tuberculous granulation were found.

### *Recognition of Gastric Tuberculosis from its Gross Picture*

One wonders, after considering the vagaries of the gross manifestations presented by gastric tuberculosis, whether there is any hope for clinical recognition of the disease, or whether one should be content with Logeais' (32) statement that "... le diagnostic est une surprise d'examen histologique." It is at once evident that, if the diagnosis is to be made prior to surgery, it must be made by roentgenographic and gastroscopic methods, that is, from the gross appearance of the lesion. No other clinical or laboratory examination gives much helpful information. In a rare disease it helps not at all to practice "statistical medicine," i.e., to put emphasis on the age and sex of the patient and similar findings. It is necessary to get much closer to the disease process, and in the case of gastric tuberculosis one can perhaps get closest with the gastroscope. The problem revolves, of course, about differentiation of gastric tuberculosis and carcinoma,

and the difficulties to be encountered here have been emphasized by all who have considered the subject. An objection to pursuit of means for preoperative differentiation of the two diseases may be raised by those who point out that the treatment of choice in either case will be surgery. But this is not a good way to circumvent diagnostic problems.

Consideration of the descriptions of the various types of gastric tuberculosis reveals that there are four peculiarities of the gross manifestations which are often presented by the disease, are seldom found in carcinoma and other malignancies, and are susceptible of recognition by gastroscopy and roentgenologic methods:

(a) The undermined edge is characteristic of a tuberculous ulcer and of no other gastric disease. A large proportion of the lesions is ulcerous. The undermining of the edges can be recognized gastroscopically. Because of gastroscopic unfamiliarity with the disease, the expected frequency of a successful conclusion on the matter is not known. This feature has not in the past been determinable roentgenographically.

(b) The ulcer is typically serpiginous in outline, its edges are often or usually violaceous in the living state, and there may be fistulous openings through the mucosa nearby. These are not features of the malignant lesion. They are peculiarities which are easily demonstrated by the gastroscopist.

(c) Whatever gross form the lesion may take, superficial tubercles are common in the neighborhood. Tubercles which elevate the mucosa are probably recognizable as such by the gastroscopist when they lie in association with a larger lesion of some sort. This is a point of considerable potential help and it may constitute the gastroscopist's only lead, as was the case in the patient described by Moersch (34).

(d) Gastric motility is disturbed less by a tuberculous process than it is by a malignant one of similar magnitude. This is a relative matter. It can be judged only by the roentgenologist.

Few other useful distinguishing features have been recognized in the gross form of the lesion. Logeais (32) was struck by the fact that the tuberculous tumor often forms a voluminous mass and that this mass ends abruptly at its proximal limits.

### THE STOMACH IN TUBERCULOUS INDIVIDUALS

It is a well-accepted fact that the gastric mucosa can reflect, by both functional and anatomic changes, the presence of acute and chronic infectious processes elsewhere in the body. Such changes are nonspecific. They may be very severe, both in their clinical manifestations and in their gross and microscopic mucosal alterations, so severe in fact that they overshadow the basic disease process. Diphtheria and scarlet fever are notably acute infections responsible for the acute endogenous gastritis, and tuberculosis is the most common cause for an infection-engendered chronic gastritis. The frequency with which the tuberculous patient complains of his upper gastrointestinal tract is well known to all who deal with the disease.

The characteristic physiologic gastric alteration of pulmonary tuberculosis is depression of gastric secretion. Achlorhydria is a frequent accompaniment of the disease. Vilardell (49) concluded, after a study of 140 tuberculous patients,

that depressed gastric secretory function is so often associated with the more serious cases that gastric analysis may provide valuable prognostic information. In reviewing the literature, however, he was forced to admit that there has been considerable discrepancy in reported studies of secretory changes. Thus, one writer found anacidity in 50 per cent of cases studied, another in 18 per cent, and a third in only six per cent. The recent investigations of Capo Porcel (10), nevertheless, seem particularly convincing. Among 100 tuberculous patients histamine-refractory achlorhydria was found in 24 and hypochlorhydria in 33. These 57 patients had more upper gastrointestinal troubles than the others but substitution therapy gave considerable relief, particularly for the anorexia, vomiting, and diarrhea. As far as the symptomatic picture in reported series is concerned, however, it is difficult to judge causal relationships because seldom have other possible sources of gastrointestinal complaints been excluded.

TABLE 6

*Gastroscopic Findings in Tuberculous Patients who Presented no Tuberculous Gastric Lesions*

| REFERENCE | NUMBER CASES | NORMAL | ULCER | CHRONIC GASTRITIS | | | |
|---|---|---|---|---|---|---|---|
| | | | | Atroph. | Superf. | Hyper-tr. | Superf.-atrophic |
| Browne, McHardy, and Wilen (8) | 50 | 19 | 8* | 12 | 11 | 0 | — |
| Flexner and Baum (22) | 26 | 5 | — | 3 | 7 | 1 | 10 |
| Hardt, Weissman, and Coulter (28) | 119 | 56 | — | 63 | 0 | 0 | — |
| Rodríguez Olleros and de la Viesca (43) | 23† | 2 | — | 3 | 11 | 7 | — |
| Totals | 218 | 82 | | 81 | 29 | 8 | |

* Of the 8 ulcers, 3 were simple benign lesions, one a malignant ulcer, and 4 were atypical ulcers which possibly were of a tuberculous nature.

† Erosions were found in 5 cases, and in 4 others the mucosa was unusually fragile, as evidenced by bleeding produced during instrumentation.

The anatomic basis for the depressed gastric secretory function in tuberculosis has been well elucidated by the gastroscopists (table 6). Of 218 tuberculous patients studied endoscopically, a normal gastric mucosa has been found in only 82. Chronic atrophic gastritis has been the most frequent abnormality, occurring in 81. In addition, the anatomic precursor of atrophic gastritis, chronic superficial gastritis, has been demonstrated in 29 and superficial-atrophic gastritis in 10. Thus, among 218 patients there were 120 cases of atrophic or preatrophic gastritis. These figures, of course, represent only a spot check of each patient during one phase of his pulmonary disease. Gutzeit and Teitge (25) believed that all those patients with significant clinical pulmonary tuberculosis who survive will eventually develop gastric atrophy. One result of atrophy of the gastric glands is, of course, suppression of normal secretory rate. Although several investigators have felt that this gastric mucosal damage is the result of a toxic process (49), Rodríguez Olleros and de la Viesca (43) probably came closer to the truth by demonstrating that the gastric changes could best be correlated with the degree

of malnutrition accompanying the tuberculous patient's chronic illness. Chronic atrophic gastritis in other situations, notably sprue and pernicious anemia, is known to have a nutritional basis, and Capo Porcel (10) has demonstrated that at least the physiologic results of the gross changes in tuberculosis can be partially reversed by nutritional means.

SUMMARY

Tuberculosis of the stomach, a rare manifestation of the infection, may be classified grossly into ulcerous, infiltrative, tumorous, and inflammatory types. Although any part of the stomach may be involved, the antrum and lesser curvature of the pars media are most frequently affected. A consideration of the gross manifestations of the lesions, as they have been described in published reports of gastroscopic, surgical, and autopsy material, suggests that specific preoperative diagnosis by the gastroscopic method may be possible in some cases. Considered to be characteristic of the gross picture are the undermining of the edges of the ulcer type, the ulcer's typically serpiginous outline, the frequent presence of nearby superficial tubercles, whatever the gross form of the major lesion, and the tendency towards slight interference with gastric motility in spite of extensive involvement of the gastric wall.

The stomach of the tuberculous patient who has no gastric tuberculosis tends to demonstrate depressed secretory activity. Gastroscopy frequently reveals a chronic atrophic gastritis, best explained as a response to nutritional deficiency.

SUMARIO

*La Tuberculosis del Estómago y el Estómago en la Tuberculosis: Reseña con Referencia Particular a la Patología Macroscópica y al Diagnóstico Gastroscópico*

La tuberculosis gástrica, rara manifestación de la infección, puede toscamente clasificarse en las formas ulcerosa, infiltrante, tumorosa e inflamatoria. Aunque puede afectar cualquier parte del estómago, el antro y la curvatura menor de la parte media son las zonas más a menudo atacadas. El estudio de las manifestaciones macroscópicas de las lesiones, tal como han sido descritas en los trabajos publicados sobre material gastroscópico, quirúrgico y autópsico, indica que, en algunos casos, resulta posible hacer, con la técnica gastroscópica, el diagnóstico específico antes de la intervención. Considerados como típicos del cuadro macroscópico son: la socavación de los bordes en la forma ulcerosa, el contorno característicamente serpiginoso de la úlcera, la frecuencia de tubérculos superficiales cercanos, independientemente de la forma macroscópica de la lesión principal, y la tendencia a afectar poco la movilidad gástrica, aun siendo extensa la invasión de la pared del estómago.

El estómago del tuberculoso sin tuberculosis gástrica suele mostrar hipoactividad secretoria, y la gastroscopia revela frecuentemente gastritis atrófica crónica que se explica mejor imputándola a deficiencia nutritiva.

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# *Case Reports*

## PULMONARY ALVEOLAR ADENOMATOSIS[1]

### Report of a Case[2]

JOHN H. MOYER

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The diagnosis of pulmonary alveolar adenomatosis is not frequently made in man. This pathogenesis of the disease is little understood, and the etiology is obscure. It has been considered to be a neoplastic disease by some writers (2, 14). Others have considered alveolar adenomatosis to be an infectious disease because the clinical course and histopathological manifestations so closely resemble benign pulmonary adenomatosis, an epizootic disease which occurs in sheep throughout the world (5, 13, 15). These opposing viewpoints and the possible implications make a consideration of the entity rather enticing. The following case is worthy of consideration because of the sparsity of clinical and pathological information available on this disease. It is believed that only if these cases are brought to the attention of both the clinician and the pathologist can this entity be placed in its proper perspective.

#### CASE REPORT

A 37-year-old white female was admitted to the hospital because of weakness and shortness of breath. Her family and past medical history were noncontributory. Except for occasional visits to southeast Canada, she had spent the last ten years within the borders of Massachusetts. Being from an urban locality she had no intimate contact with rural areas, nor had she been in close proximity to sheep for at least ten years.

Her present illness began with a severe cold which lasted about three weeks. This left her with a residual cough of two months' duration. The cough was unproductive until four weeks before admission. At this time the patient noted small amounts of yellowish-white, frothy sputum. It was never brown or blood-streaked and had no odor. About two weeks later she noted increasing malaise and dyspnea, and by the time she came into the hospital complete bed rest had become necessary. She had no fever or chest pain.

Physical examination was essentially negative except for flatness to percussion and rales at the right base. Breath sounds were increased over the same area. The temperature was 99°F. There was no clubbing of the fingers or toes.

*Laboratory studies:* Repeated sputum studies for tuberculosis and fungus infection were negative on smear, culture, and guinea pig inoculation. Routine urinalyses were negative. Blood studies revealed an erythrocyte count of 4.3 million and a white cell count of 7,200 per cu. mm. with a differential count of 64 per cent polymorphonuclear cells, 32 per cent lymphocytes, and 4 per cent monocytes. The erythrocyte sedimentation rate was 30 mm. per hour by the Wintrobe method. The blood urea nitrogen was 14 mg. per 100 cc.

Roentgenographic studies showed increased lung markings in all lung fields. In the lower part of the right hemithorax a flocculant, structureless density was noted which obliterated all normal lung markings. A bronchogram revealed no abnormalities. Due to the uncer-

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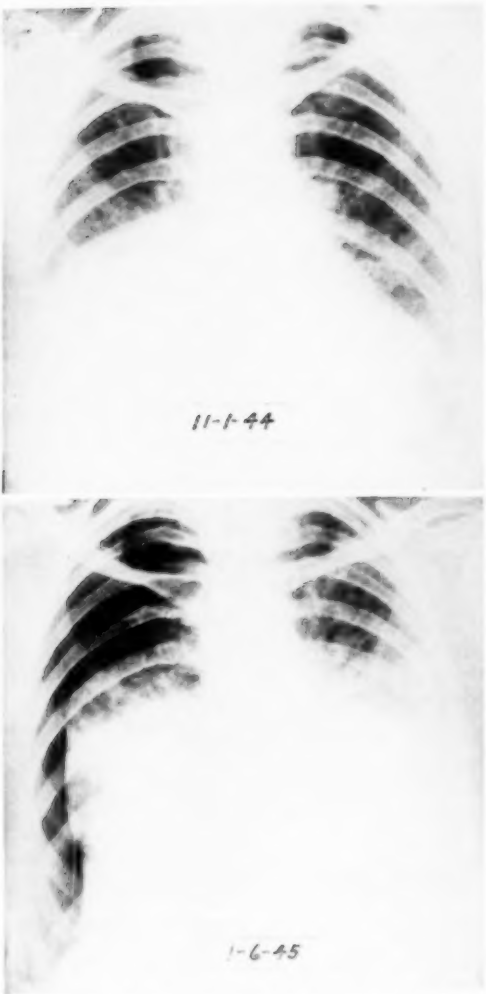


FIG. 1. (Upper) Admission roentgenogram of the chest showing increased linear markings extending out from both hili and a flocculent, structureless parenchymal infiltration with a hazy border involving the right lower lobe.

FIG. 2. (Lower) Diagnostic pneumothorax showing no evidence of involvement of the pleura adjacent to the parenchymal disease.

tainty of the exact nature of the lesion, a diagnostic pneumothorax was done. The pleurae separated readily, revealing that the disease was entirely restricted to the parenchyma

of the right lower lobe. There were no pleural adhesions. A bronchoscopic examination was negative. The vital capacity was 30 per cent of normal.

*Hospital course:* The patient's course was progressive and debilitating so that by the third week she was unable to get out of bed unaided. Dyspnea but not cyanosis became severe and weight loss was marked. Fever was not remarkable at any time. Roentgenographic studies after one month revealed a process in the left lower lobe which originated first at the base and then spread to involve the entire lobe. This was similar to the infiltration on the right. The patient died after four months in a debilitated condition.

*Post-mortem examination:* The body appeared very emaciated. Evidence of marked passive congestion was present in the spleen, kidneys, and liver. The heart was dilated and flabby. The pleura appeared normal. There were no pleuritis or pleural adhesions. The right lung weighed 1,400 Gm., the left 1,325 Gm. Both lower lobes appeared quite firm and nodular on palpation. Crepitation was markedly decreased as compared to the normal. On palpation no abnormalities of the upper lobes were noted. On section, the lower lobes cut with increased resistance. The gross appearance at the apices was that of gray, disseminated, miliary-type lesions without evidence of caseation or necrosis. As one approached the bases, the lesions became more numerous with apparent coalescence. The bases of both lower lobes consisted of solid, homogeneous, gray, pneumonic consolidation. The bronchi appeared normal but were filled with a pink, frothy, mucinous material. There were no cavities.

Microscopic studies confirmed the disseminated miliary lesions as the basic pathological process which were much more marked in some areas than others, and coalesced towards the bases of the lower lobes. The upper lobes likewise contained numerous lesions which were not visible macroscopically. In the diseased areas the alveoli were expanded and were lined with nonciliated epithelium. The cells ranged in height from cuboidal in some areas to columnar in others. In any one alveolus the height of the cells was uniform. The cellular cytoplasm was granular and slightly acidophilic. The nuclei were oval, finely reticulated, somewhat vesiculated, centrally placed, and basophilic. There were one to 3 nucleoli present in each nucleus. The nuclei of the cells lining the alveoli stained more darkly than those of the bronchial epithelium. In areas of alveolar involvement the neighboring bronchi showed some thickening of the basement membrane. A few of the smaller (respiratory) bronchioles showed epithelial thickening with cellular stratification adjacent to involved alveoli. Although suggestive of a transitional phase, it was felt that these findings could not be interpreted as definite evidence of the bronchogenic origin of the pathological cells. Except for minimal interalveolar fibrosis, the alveolar stroma was not altered. There was no invasion of this stroma by the cells lining the alveoli. In many areas the cells showed the results of extreme proliferation manifested by papillary infoldings. *Mitotic figures were remarkable for their absence, even in areas of most active proliferation.* Some alveoli also contained mucoid material and inflammatory exudate consisting of lymphocytes and polymorphonuclear leukocytes. Also, lymphocytes were seen occasionally in apparently normal alveoli. There was excessive perivascular and peribronchial infiltration of lymphocytes. There was *no* evidence of invasion of blood vessels or of the peribronchial and mediastinal lymph nodes by the pathologically proliferating intra-alveolar cells.

The diagnosis was pulmonary alveolar adenomatosis.

## DISCUSSION

As the clinical course and histopathological manifestations which this patient presented are compatible with a diagnosis of pulmonary alveolar adenomatosis, some questions are immediately suggested: (*1*) Is pulmonary adenomatosis an infectious disease and if so, is it allied to the epizootic disease, benign pulmonary adenomatosis, in sheep? (*2*) What is the origin of these proliferating epithelial cells within the alveoli? (*3*) If alveolar adenomatosis in man is a primary neoplasm of the lung, possibly of bronchogenic origin, is it benign or malignant?

There is certainly a great similarity between the clinical and histopathological manifestations of pulmonary adenomatosis in man and its ovine counterpart, epizootic benign pulmonary adenomatosis. For this reason a consideration of the latter, a much better established entity, seems to be in order. The ovine disease has been known by many different names throughout the world. In England it has been known as verminous pneumonia, in South Africa as Jaagziekte, in Iceland as benign alveolar adenomatosis, and in Montana (United States) as progressive pneumonia. The disease has destroyed up to 85 per cent of the sheep population during epidemics in some areas (15). Similar histopathological entities have been reported in horses (5) and guinea pigs (11). No relationship of the etiological agents in these different species has been found nor is there any evidence that the disease has been transferred from one species to another. Although the etiological agent of the ovine disease has not been isolated, there seems to be little doubt among investigators in this field that it is an infectious agent, possibly a filterable virus (5, 6, 7). Despite the fact that direct transmission of benign pulmonary adenomatosis by other than intra-pulmonary injection in an isolated instance (7) has proved fruitless, sheep free of disease which are housed together with infected sheep almost invariably contract it. An epidemic in Iceland, where the disease was unknown prior to 1933, was traced to a diseased ram which was imported from Germany. The period between contact and clinical manifestations has been about six to eight months (7). Cold wet weather, crowding, and poor housing appear to aid in the transmission of the disease, and to hasten its course.

No similar observations of the transmissability of pulmonary alveolar adenomatosis in man have been made, nor has there been any reason to suspect the transmission of the disease from animal to man. Reported cases have been sporadic and apparently spontaneous. Attempts at culture of an etiological agent in bacterial culture media, virus culture media, and laboratory animals have all proved fruitless (13, 15).

The clinical course of the ovine disease is quite characteristic. The onset is very insidious, no symptoms being evident until the pathological process is well advanced. The first symptom that usually appears is an occasional cough which later becomes spasmodic and prolonged. The animals become less active and develop progressive dyspnea. However, the clinical course is afebrile until the terminal state, when secondary infection may occur. Increasing amounts of frothy, watery, mucus are secreted from the nostrils. "Wet" rales, which are at first heard only on auscultation, become quite audible so that they can be detected at some distance from the animal. In the far advanced state, the sheep become anorexic and debilitated. In a severe cachectic state, death rapidly ensues. The total duration of the disease, from onset of symptoms to death, varies between two weeks and a year. The mortality rate is no less than 95 per cent (7).

The clinical course of pulmonary alveolar adenomatosis in man, in contrast to the transmission of the disease, is almost identical with the ovine disease. Leukocytosis and clubbing of the fingers and toes have been additional observations (13). The roentgenographic picture is one of an increasing and progressive pulmonary infiltration. The lesions are at first localized and miliary, later becoming flocculant. An appearance of consolidation similar to lobar pneumonia finally develops. Cavitation has been reported in one case (15).

Alveolar adenomatosis in man and the ovine disease present almost identical gross and microscopic pathological manifestations. In both, the basic alteration is a proliferation of epithelial cells within the alveoli in such a manner as to completely line the alveoli. As the proliferation continues these cells pile up, forming papillary folds. In spite of the rapid proliferation, there is very little evidence of mitosis, and the alveolar stroma is not invaded. The cells are cuboidal or columnar, and quite uniform in size without evidence

of anaplasia. Inflammatory cells are rarely present unless secondary infection has taken place. The nuclei are uniform and usually basophilic. The cytoplasm is granular and acidophilic. Vascular invasion and metastases are not a part of the disease although regional lymph node invasion has been reported in the human disease (3, 12) as well as in the epizootic disease in sheep (case report by Aynaud and cited by Sims (13)). These similar pathologic manifestations are the main claim for considering that both of these diseases have a common etiology. It seems quite possible, however, that both entities represent a common tissue response to two fundamentally different processes, the ovine variety being infectious and the human being neoplastic. The possibility that an infectious agent might be the etiological basis of a neoplasm in man, as it might well be considered to be in sheep, is a very interesting one for speculation. From the information available, however, there seems to be no evidence to support the notion of an infectious origin of the disease in man. The similarity of clinical manifestations lends little aid to clarification of this problem since it is a common observation that the manifestations of pulmonary disease are more dependent upon the mechanical alteration of function than upon the basic cause of this alteration. Indeed, in view of the similar histopathologic changes in both diseases, it would be more surprising if the clinical manifestations were not similar.

Whether the origin of these pathologically proliferating cells is bronchogenic or alveolar is open to the same controversy as is the origin of "alveolar cell carcinoma." Miller (10) has used the presence of epithelial-like cells lining the alveoli in certain pathologic states of the lungs as valid proof of the existence of alveolar epithelium. In addition, it seems to be the opinion of numerous investigators that the proliferating cells in the epizootic disease in sheep, as well as in alveolar adenomatosis in man, are of alveolar origin (1, 4, 7, 12, 13, 15).

On the contrary, Herbut (9) denies the presence of alveolar epithelium. He has been able to demonstrate by serial sections that regeneration of epithelium takes place from the epithelium of the respiratory bronchioles and not from septal cells. He also denies the alveolar origin of any pulmonary neoplasms. These conclusions are further supported by Fried (8) who believes that, despite the occasional occurrence of epithelial cells in the alveolar walls, these walls are actually bare of epithelium, which in itself precludes the alveolar origin of neoplastic tissue.

If enough serial sections are made, there seems to be adequate evidence to make the bronchogenic origin of adenomatosis a plausible consideration. Cowdry (4), although concluding that the proliferating cells of the ovine disease were alveolar in origin, found proliferation of bronchial epithelium in some areas. Bonne (2), by serial section of the diseased lung in a patient meeting the histopathologic requirements of alveolar adenomatosis, found a continuation of the cells lining the alveoli with similar cells which lined the adjacent respiratory bronchioles in many areas. Sweany (14) observed local implantation of neoplastic cells within the alveoli spreading out from the smaller respiratory bronchioles in a case with histopathologic manifestations of alveolar adenomatosis. In the case being presently reported, there was enough evidence in the form of epithelial thickening, in some respiratory bronchioles adjacent to involved alveoli, to suspect a transitional phase of the bronchial epithelium to the proliferating cells lining the alveoli, or vice versa. In view of these observations, it seems quite possible that the primary site of the epithelial proliferation is the smaller respiratory bronchioles. Furthermore, in the absence of any evidence to support an infectious basis for alveolar adenomatosis in man, it is quite reasonable to assume that this disease in man is neoplastic. However, none of these observations can be considered conclusive.

If alveolar adenomatosis in man is a primary neoplasm of the lung, possibly broncho-

genic in origin, is it benign or malignant? Insofar as the patient is concerned, the disease is certainly malignant, since in reported cases the mortality has been 100 per cent. However, from a descriptive histopathologic point of view the disease is benign since it allegedly does not metastasize; the pathologic cells are uniform in size, do not invade, and show no evidence of mitosis. However, these accepted allegations are not strictly true. For example, in a case reported by Sweany (14) and one by Briese (3), typical histologic descriptions of "alveolar cell adenomatosis" were accompanied by single metastases to regional lymph nodes in each case. Further, Obendorfer (12) found a bony metastasis in addition to a regional metastasis in a similar case. Sweany (14) observed what he interpreted as implantation of neoplastic cells within the alveoli by direct respiratory spread, and a hilar node metastasis in the same patient. Mitotic figures were rare in these instances. However, Bonne (2) reported a case showing numerous mitotic figures, but no metastatic lesions. Are these cases of "alveolar adenomatosis," or are they carcinoma as classified by Sweany? Bonne (2) has aptly termed this pathologic entity "carcinosis," suggesting that "alveolar cell carcinoma" might be considered the connecting link between "adenomatosis" and ordinary bronchogenic carcinoma. Thus, there can be visualized a continuous histopathologic variation from typical bronchogenic carcinoma to a very atypical form, adenomatosis, of the same malignant process. If the disease invades and metastasizes, it kills by this metastatic localization in addition to the local process and its complications so typical of bronchogenic carcinoma. Contrariwise, if the disease remains localized, as occurs in alveolar adenomatosis, it kills by the progressive loss of pulmonary function alone.

SUMMARY

1. A case of pulmonary alveolar adenomatosis in a 37-year-old female patient is presented which resulted in progressive respiratory insufficiency and death.

2. The similarities to progressive pneumonia (benign pulmonary adenomatosis) in sheep are discussed. The disease, pulmonary adenomatosis, is probably infectious in sheep but apparently is not so in man. The histopathologic manifestations and clinical courses of the disease in man and in sheep are quite similar. This is as far as the similarity goes. These entities probably represent a common tissue response to widely different etiological agents.

3. There seems to be sufficient evidence to suggest a similar origin (bronchial or alveolar) for the proliferating cells in both entities.

4. Pulmonary alveolar adenomatosis in man is possibly an atypical form of bronchogenic carcinoma similar to "alveolar cell carcinoma" but with less histopathologic evidence of its proliferating abilities. Because of the low-grade malignant character, metastases and tissue invasion are found only in the exceptional case.

SUMARIO

*Adenomatosis Alveolar Pulmonar*

1. El caso descrito es de adenomatosis de los alvéolos pulmonares en una mujer de 37 años, culminando en insuficiencia respiratoria progresiva y la muerte.

2. Discútense las semejanzas con la neumonía progresiva (adenomatosis pulmonar benigna) de las ovejas. La adenomatosis pulmonar es probablemente infecciosa en las ovejas, pero aparentemente no es así en el hombre. Las manifestaciones patológicas y evolución clínica son bastante similares en el hombre y las ovejas. Hasta ahí va la semejanza. Esas entidades representan con toda probabilidad la reacción de un tejido común a agentes etiológicos muy distintos.

3. Parece que hay suficientes datos indicativos de un origen semejante (bronquial o alveolar?) de las células proliferantes en ambas entidades patológicas.

4. La adenomatosis alveolar pulmonar en el hombre es posiblemente una forma atípica de carcinoma broncógeno, semejante al "carcinoma de las células alveolares," pero con menos signos histopatológicos de su capacidad proliferante. Debido a su escasa malignidad, sólo se observan metástasis e invasión histológica en los casos excepcionales.

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# MILIARY TUBERCULOSIS[1]

## Report of a Case of Long Duration without Chemotherapy

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The physician in student health work must be constantly alert for the case that bursts the bounds of usual behavior and leads a merry chase over fields of diagnostic possibilities. Particularly is this true when epidemics of colds, intestinal upsets, and the like invade the campus. One case illustrating this point is well worth reporting since its unusual features were so camouflaged by a mild epidemic of grippe that it did not become apparent immediately that the behavior pattern was at variance to the other cases.

### CASE REPORT

The patient was a male student, twenty-three years of age, and single. Born in Canada of Syrian parents he moved to the United States when thirteen years old. He entered Princeton University in September 1942, but withdrew in February 1943 to join the army. After basic infantry training, he was put in the A.S.T.P. at North Carolina for one term. He spent eighteen months in the European Theatre of Operations in England, France, and Germany and was discharged without disability in January 1946. Roentgenograms of the chest on admission and discharge were clear. There was little of note on his freshman physical examination at the University except that the skin reaction to tuberculin was negative. The patient had enjoyed good health all of his life except for an attack of rheumatic fever at the age of twelve from which he made a complete recovery after six months in bed. His family history was negative for tuberculosis.

The patient re-entered the University March 1, 1946 and was admitted to the infirmary on March 19, complaining of fever and headache. His illness had begun four days before with headache across the forehead, malaise, and insomnia. These symptoms had increased in severity, and waves of dizziness had been experienced. A transitory diarrhea had developed on March 17, and he had noted chilliness on going out of doors. There was no cough and no sore throat.

The temperature was 104.2°F. and the pulse 100 and of good volume with no irregularities. The skin was hot and dry, but no rash was visible. The pharynx was slightly infected. Examination of the heart and lungs was negative. The abdomen was soft and flat with no palpable masses. The neck was relaxed and there were no enlarged lymph nodes. A specimen of urine was negative except for a one plus albumin which did not appear in subsequent tests. The total leukocyte count was 5,350 cells per cu. mm. and the differential percentages were: polymorphonuclear leukocytes, 74; lymphocytes, 24; and mononuclear leukocytes, 2. A tentative diagnosis of "grippe" was made and he was put to bed on Empirin compound, 0.3 Gm. every three hours with an occasional dose of codein.

The temperature remained over 102°F. for three days except at noon of each day, when it regularly dropped to 99°F. After the third day the temperature gradually receded until the eleventh day, after which it demonstrated a marked tendency to stabilize at 98°F. in the morning and approximately 100°F. in the late afternoon. This was the first indication that the case was different from the typical "grippes" inhabiting the infirmary. The administration of penicillin had no effect upon the temperature. The patient had no complaint after the fifth hospital day. Determinations of the total leukocyte counts on the average of every third day varied between 7,000 and 4,400 cells per cu. mm. The type of cells started to shift on the eighth day. The polymorphonuclear leukocytes gradually

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dropped to 40 per cent; the lymphocytes rose to 42 per cent; and the mononuclear leukocytes, to 14 per cent, with eosinophils 3, and basophils 1. Serum agglutination reactions for undulant fever, typhoid H and O, and paratyphoid A and B were negative. The erythrocyte sedimentation rate (corrected) was 9.5 mm. The concentration of hemoglobin and the total erythrocyte count were normal. The Vollmer patch test was positive and chest roentgenograms on the fifteenth hospital day revealed a fine, nodular infiltration throughout the parenchyma of both lungs (figures 1, 1a, and 1b). The lungs were clear to percussion and auscultation and there were no cough or sputum. The roentgenographic finding and the change in the tuberculin test were so suggestive that a tentative diagnosis of miliary tuberculosis was made.

Arrangements were completed for the patient to be transferred to his own home where he spent nine weeks in bed. During this period he felt fine, gained ten pounds in weight, and was symptom-free, although he continued to run a late afternoon temperature of about 100°F. His maxillary sinuses were a little cloudy on transillumination, and they were irrigated. The procedure had no effect on his temperature and in late June he was admitted to a sanatorium for observation and study.

The preliminary report issued ten days after admission recorded a well-developed and well-nourished patient who was not apparently ill. The pharynx was reddened. The frontal sinuses illuminated poorly, but the antra appeared fairly clear. There was slight impairment of the percussion note over both lungs above the clavicles. Examination of the heart and abdomen was negative. The left lateral lobe of the prostate was somewhat fibrosed. There was a small tumor over the middle joint of the left index finger. The temperature ranged between 98.5° and 100°F.; and the pulse 70 to 90 per minute; with the blood pressure 128 systolic, 78 diastolic in mm. of mercury. The erythrocyte sedimentation rate was 15 mm., and a serologic test for syphilis (Mazzini) was negative. A skin test with PPD was one plus to the first dose. The concentration of hemoglobin was 87 per cent. The erythrocytes numbered 4,800,000 and the leukocytes 5,200 cells per cu. mm. with differential percentages: polymorphonuclear leukocytes, 70; lymphocytes, 18; mononuclear leukocytes, 11, and eosinophils, 1. A chest roentgenogram revealed that the fine, nodular infiltration present before admission had largely cleared. No definite diagnosis was made at this time.

At the end of ten weeks the sanatorium reported that the patient had been in bed since admission and that there had been no marked change. His temperature ranged between 99°F. and 100°F. during the first month and for the previous four weeks the maximum temperature had seldom been below 100°F. The pulse had been 80 to 95 and the weight had not varied more than one pound. The patient continued to look and feel well, and there had been no cough or expectoration. Material from gastric lavage had been negative for tubercle bacilli on culture and guinea pig inoculation. The spleen had enlarged and varied in size at repeat examinations. Two blood cultures for aerobes and anaerobes had been negative. Thick and thin malarial smears, stools, and stool cultures had revealed no abnormal findings. The agglutination serum reactions in the seventh week showed:

Typhoid O, slight in 1 to 80
H, 4 plus to 1 in 40; 3 plus to 1 in 60
Paratyphoid A, 2 plus to 1 in 40; 1 plus to 1 in 160
B, 2 plus to 1 in 40; 1 plus to 1 in 80 Brucella, negative in all dilutions.

These tests had been repeated in the eighth week and the only change was that the typhoid H agglutination was 3 plus in the 1:40, and 1 plus in the 1:60, dilution. These findings were considered to be consistent with previous typhoid inoculations which the patient had had in the army. The blood counts had remained about the same with erythrocytes 4,900,000, leukocytes 6,500 cells per cu. mm. with differential percentages: polymorphonuclear leukocytes, 72; lymphocytes, 16; mononuclear leukocytes, 10; eosinophils, 1, and basophils, 1. The hemoglobin concentration was 91 per cent. Three sets of chest roentgenograms (admission, seventh week, and tenth week) were reported as failing to show the infiltration noted at the beginning of his illness.

The diagnosis remained obscure and it was believed that a special survey was in order.

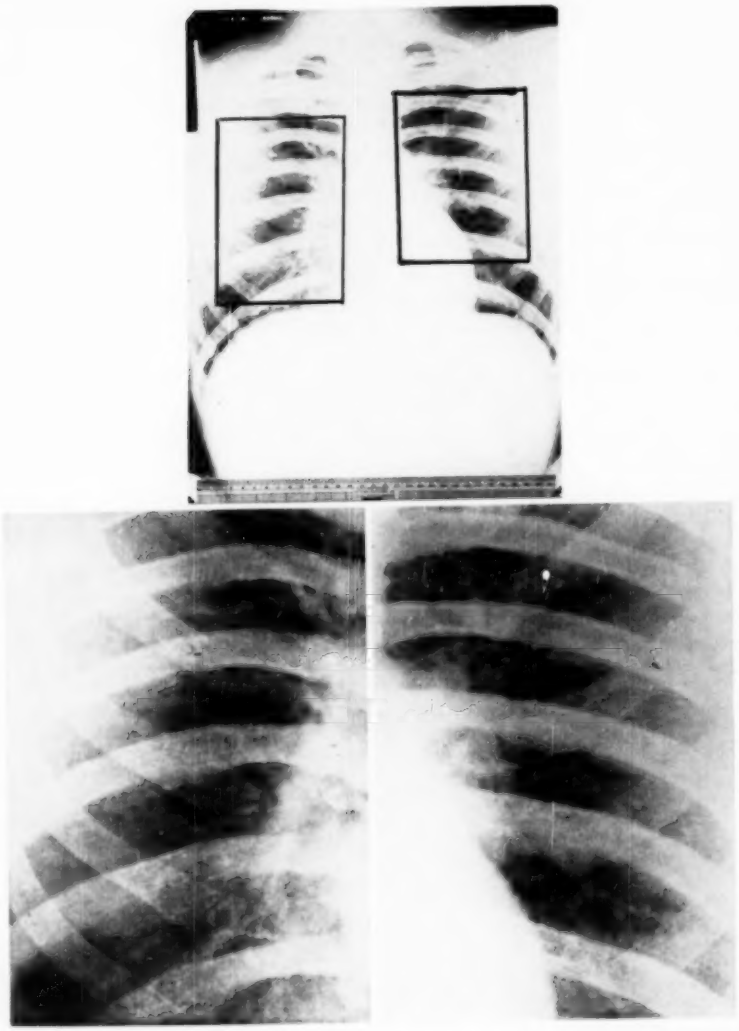

FIG. 1. (Top) Taken about three weeks after start of illness showing the generalized character of the infiltrative process.

FIG. 1a. (Lower left) Enlarged section from the right lung field in figure 1 showing the process in detail.

FIG. 1b. (Lower right) Enlarged section from the left lung field in figure 1 showing the process in detail.

Accordingly, the patient was transferred to a private hospital where the following laboratory determinations were obtained: an erythrocyte sedimentation rate of 32 mm.; two sterile blood cultures; normal values for total serum protein and nonprotein nitrogen; negative Widal, dysentery, and Brucellus agglutinations; negative histoplasmin and brucellergin skin tests, and normal values for hemoglobin and total erythrocytes. The urine examination was negative except for one plus albumin. Interpretation of the chest roentgenograms lead to the presumptive diagnosis of Boeck's sarcoid despite the normal total serum protein, and it was recommended that the patient be permitted to resume his studies.

At home two specimens were taken from the swelling on his index finger and sections were made on October 26. One showed a vascular granulomatous tissue containing giant cells with multiple nuclei suggestive, but not diagnostic, of Boeck's sarcoid. Examination of the other specimen revealed no significant findings. On November 9 the patient's serum albumin was 4.5 and the globulin 3.1 Gm. per 100 cc. The total serum protein was 7.6 per 100 cc. The value for uric acid was normal and a serological test for syphilis was negative. In the meantime he had developed a fusiform swelling above the right patella which, together with the lung picture, was interpreted to be consistent with a diagnosis of Charlemagne's disease, and a good prognosis was given. The swelling subsided in November but flared up for a short spell following an operation in late January 1947 for a pilonidal cyst which started in early December.

The patient returned to the University to take up his studies the first week in March 1947, at which time a chest roentgenogram was made which showed no evidence of the original process (figure 2). He reported every other day for dressings on his operation wound which finally cleared on March 21. The afternoon temperature was usually slightly above 99°F. and the patient felt and looked quite normal during these two weeks.

On March 26, one year and a week after the start of his illness, he came to the infirmary requesting permission to go home, as he felt exactly as he did originally. His temperature was 99.4°F. He reported immediately to his family doctor who put him on sulfadiazine without benefit. He developed a severe photophobia and slight rigidity of the neck on March 31, and was taken to the hospital where a roentgenogram showed that the lungs were apparently clear. A consulting neurologist believed, on the basis of the neurological findings and spinal and cisternal taps, that the patient had a meningitis with a cervical or spinal block. The differential diagnosis still rested between Boeck's sarcoid and tuberculosis as the causative agent, with the former being favored because the bacillus of tuberculosis had not been obtained. The patient's condition steadily became worse, and he died on April 12, 1947 with a clinical diagnosis of "pachyleptomeningitis, diffuse, cause undetermined." The relevant details from the report of the post-mortem examination are presented below.

*Anatomical diagnosis:*

leptomeningitis—spinal
internal hydrocephalus
caseous lymph node—mediastinum
passive congestion of lungs
anemic infarcts in kidneys

*Pleural cavities:* Both pleural cavities were free from fluid and adhesions.

*Lungs:* Both lungs were voluminous and almost filled their respective pleural sacs. The lower lobes were dark red and moderately firm and the upper lobes were pale gray and crepitant. Two small nodules were palpable just beneath the pleura of the lower part of the right upper lobe. These nodules were grayish-yellow on section. The upper lobes of both lungs were pale gray on section and the lower were dark red and edematous. No areas of consolidation or focal lesions were visible in the lower lobes. Just to the left of the tracheal bifurcation there was a lymph node 1.0 by 1.5 cm. in size which was pale yellow and caseous on section. Two small nodes were palpable beneath the pleura of the hilus of the right lung. They were pale reddish-gray on section.

*Pericardium:* The pericardial sac was of about normal size and shape. There was no free fluid in it and the sac was not adherent to the heart.

*Heart:* The heart was of normal size and shape and appeared normal externally. All of the valves and valve orifices appeared normal and the endocardial surfaces were smooth in the auricles and ventricles. Both coronary arteries were of normal size and their walls were of normal thickness. There were no gross changes in the myocardium.

FIG. 2. Taken about a year later than figure 1 showing complete clearing.

*Abdominal cavity:* There was no free fluid in the peritoneal sac and the organs appeared normal.

*Liver:* The liver was of normal size and shape, pale reddish-brown externally, and the capsule was smooth. On section the cut surfaces were of the same color and the lobular pattern appeared normal.

*Spleen:* The spleen was of about twice normal size and was smooth and purplish-gray externally. On section, the cut surfaces were pale red. The splenic follicles were of about

normal size and the pulp was firm. No focal lesions or tubercles could be made out on gross examination.

*Kidneys:* Both kidneys were of about normal size. Several pale yellow infarcts were visible beneath the capsules of both. No tubercles or focal lesions were visible in the renal substance.

*Adrenals:* Both adrenals were of normal size and shape. They were normally pigmented on section.

*Head:* The scalp and skull were normal in appearance.

*Dura:* The dura was of normal color and thickness. When it was incised, no excess fluid escaped.

*Brain:* There was marked flattening over both hemispheres with broad gyri and shallow sulci. The pia-arachnoid was thin and transparent over the convex surfaces. Most of the base of the brain was of similar appearance. Beneath the floor of the third ventricle and about the optic chiasma, the soft meninges were edematous and contained increased fluid. No lesions suggestive of tubercles could be made out. In the posterior cranial fossa the pia-arachnoid of the cerebellum and medulla were of essentially normal appearance. A section through the brain parallel to the base and about through the middle of the thalamus showed marked edema of the brain substance. All of the ventricles were dilated and contained clear fluid.

*Spinal cord:* On opening the spinal canal the spinal dura was of normal color and thickness but appeared to be under increased tension. When the dura was incised there was excess fluid within it. From about the third cervical vertebra down to the cauda equina, the soft meninges of the cord were thickened and had a mucinous appearance. Tubercles or purulent exudate were not visible. There were no gross adhesions to the spinal dura. Sections through the cord showed thickening of the pia-arachnoid. The central canal was not visible.

### *Histological Examination*

*Mediastinal lymph node:* A mediastinal node about 1.0 by 1.5 cm. in size was almost completely caseous. Tuberculous granulations in which there were numerous giant cells surround the caseous area.

*Right kidney:* An infaret-like lesion in the renal cortex was caseous and there were tuberculous granulations about it with scattered reticulated tubercles in them.

*Brain and spinal cord:* Sections from the convex surfaces of the brain showed diffuse but scanty infiltration of the pia-arachnoid by lymphocytes and larger mononuclear cells. Over the base and especially in the interpeduncular space, inferior surface of the pons, there was a thick layer of exudate in and on the pia-arachnoid. It was composed of fibrin, large mononuclear cells, and lymphocytes. Small points of necrosis in the exudate suggested early tubercle formation.

About the brain stem and cord there was a similar exudate but of much greater thickness. Below foramen magnum, the exudate surrounded nerve roots and extended into the substance of the cord around small vessels. There were marked degenerative changes in the nerve roots. Cellular infiltration extended into the substance of the cord along nerve roots and blood vessels in the thoracic portion of the cord. A few imperfect tubercles were recognizable in the exudate about the cervical portion of the cord.

*Bacteriologic studies:* Virulent tubercle bacilli were cultivated from the cerebrospinal exudate.

*Diagnosis:*

tuberculous leptomeningitis—cerebral and spinal
caseous lymph node—retrobronchial
caseous foci in kidneys

### COMMENT

The post-mortem bacteriologic and histologic findings prove that the patient died of a tuberculous infection centering in the central nervous system. This naturally forces

attention to be focused upon the original ailment a year earlier. The young man's illness resembled ordinary "grippe" which was prevalent on the campus at the time, but the temperature curve showed afternoon humps beyond the usual period of recovery. In seeking a reason, the only definite finding was a change in the tuberculin test to positive. As a consequence, the chest roentgenograms were obtained. These demonstrated the fine, nodular process throughout both lungs. In the light of the autopsy record, these lesions were undoubtedly miliary tuberculosis as originally suspected. However, the patient's appearance, relative lack of symptoms, and the rapid clearing of the lungs in subsequent roentgenograms forced this diagnosis into the background in favor of Boeck's sarcoid. As repeated attempts to isolate *M. tuberculosis* failed, the diagnosis of Boeck's sarcoid seemed even more likely. Thus the possibility of sarcoid disease with a favorable prognosis served to prevent recognition of the quiescent stage of a tuberculous infection which eventually became complicated by a fatal meningitis.

## AMERICAN TRUDEAU SOCIETY

### Medical Section of the National Tuberculosis Association

THIOSEMICARBAZONE THERAPY OF TUBERCULOSIS IN HUMANS[1]

During September 1949 the writers had the privilege[2] of reviewing the results obtained in ten German institutions during the previous two years from the treatment of clinical tuberculosis with 4-acetylaminobenzaldehyde thiosemicarbazone. This drug was originally designated by the code TbI/698, and is now known in Germany by the trade name Conteben[3]. An opportunity was also afforded us to review with Professor Domagk the experimental evidence which had led to the extensive clinical trials which have been undertaken.

At the time of the review there were reported to be more than 300 hospitals and sanatoriums participating in the clinical trials of Conteben and it was estimated that more than 7,000 patients had received treatment with the drug. The institutions chosen for review were among those which had employed the drug since 1947, and which had superior facilities and directors with excellent scientific standing. The hospitals were in widely separated areas of the Western zones of Germany including the northeast, central west, southeast, and southwestern sections of the country. Also efforts were made to include visits to physicians and surgeons with various interests in different aspects of the problem under study. In the ten institutions included in the survey, a total of more than 2,000 patients had received the drug, usually for prolonged periods of time.

The following is a list of the institutions in the order visited and the names of the responsible directors.[4]

Elberfeld Municipal Hospital (near Cologne)—Professor Klee (more than 300 cases)

Essen Municipal Hospital—Doctor Heymer (approximately 300 cases)

Tonscheide Sanatorium (north of Hamburg)—Doctor Heim (approximately 50 cases)

Molln Sanatorium (near Lubeck)–Professor Kuhlmann (more than 400 cases)

University of Bonn—Professor Martini (181 cases analyzed)

Falkenstein Sanatorium (near Frankfort on the Main)—Doctor Malluche (approximately 350 cases)

Lindenburgh Sanatorium[5] (near Lake Constance) (for men only)—Doctor Brecke

Ueberruh Sanatorium near Lake Constance) (for women only)—Doctor Boehm (245 cases analyzed)

[1] This communication is a report submitted *to* the Clinical Subcommittee of the Committee on Medical Research and Therapy by the writers and hence does not represent an official report on the subject *by* the Clinical Subcommittee.

An official report on the status of thiosemicarbazone therapy is being prepared by the Subcommittee and will appear in an early issue of the Review.

[2] We are indebted to Doctor Charles Dutchess, Medical Director of the Schenley Laboratories and to Doctor Anton Mertens, Scientific Director of the Bayer Company, who with their respective organizations made this survey possible.

[3] Proposed proprietary names in the United States: "Tibione" (Schenley Laboratories Inc.) and "Myrizone" (E. R. Squibb and Sons).

[4] The fine hospitality of the directors named, their unstinted efforts aided by the excellent cooperation of their assistants in preparing data, presenting representative case history charts, roentgenograms, and actual patients, made the journey a pleasant one and extremely rewarding in terms of quantity and quality of scientific data assembled.

[5] Lindenburgh Sanatorium was not actually visited but the data were brought to near-by Ueberruh Sanatorium and presented to us by Doctor Brecke, director of the Lindenburgh Sanatorium.

Grengland Sanatorium, St. Blasien (Black Forest region)—Doctor Schaich
University of Freiberg[6]—Professor Heilmeyer
(231 cases analyzed)

The total number of cases treated with thiosemicarbazone in the above institutions was approximately 2,000.

*Experimental Background*

Domagk has published evidence that the thiosemicarbazones are effective *in vitro* and *in vivo* against the tubercle bacillus and against tuberculosis produced experimentally in guinea pigs and rabbits. Levaditi has shown that Conteben is effective against tuberculosis produced experimentally in mice. The latter concluded that in mice the restraining influence of Conteben is comparable to that exerted by para-aminosalicylic acid. It is not possible to compare the results in guinea pigs with those which may be obtained with treatment of the experimental disease by Promin, Promizole, streptomycin, or para-aminosalicylic acid. It is the tentative opinion of one of us (H.C.H) that Conteben is less effective than the other drugs named, but this relationship cannot be established until parallel series of studies are completed. Methods of experimentation have been developed which should make an estimation of this comparison possible.[7]

*Dosage*

Conteben is tolerated by experimental animals much more readily than it is by human beings. Domagk states that mice will tolerate prolonged treatment with as much as 5.0 Gm. per Kg. per day orally. In contrast, humans will tolerate only about 0.005 Gm. per Kg. per day (equivalent to 0.35 Gm. for a person weighing 70 Kg.). In other words, mice and guinea pigs tolerate from 100 to 1,000 times as much of the drug, if computation is made on a body weight basis. The potential fallacies of such figures are well recognized, but since methods have only recently been developed for determination of thiosemicarbazone concentrations in body fluids, no other basis for comparison is available.

The clinicians visited were not in complete agreement as to what constituted the optimal daily dose. The recommendations ranged from a low of 0.0125 to 0.025 Gm. of Conteben per day (Heim) to 0.1 to 0.3 Gm. per day (Klee and Martini). In general, an initial dose of 50 mg. per day for one or two weeks with gradual increase to 200 mg. per day was recommended. A maintenance of constant blood levels was not considered to be essential and oral doses were given from one to four times daily.

All clinicans agreed that very prolonged treatment was desirable, the average recommendation being perhaps six months, although some patients have been treated continuously for more than a year.

*Manifestations of Toxicity*

*Gastrointestinal:* Anorexia, malaise, and occasional vomiting appeared to be the principal factors limiting dosage. These symptoms subsided when the dose was reduced or treat-

[6] Professor Heilmeyer brought his data from the University of Freiburg clinics to St. Blasien where these were reviewed.

[7] Since this report was prepared, two articles have appeared on the subject of the thiosemicarbazones in experimental tuberculosis. (Donovick, R., and Bernstein, J.: On the action of thiosemicarbazones in experimental tuberculosis in the mouse (Letters to the Editors). Am. Rev. Tubere., October 1949, 60: 539); and Hoggarth, E., Martin, A. R., Storey, N. E., and Young, E. H. P.: Studies in the chemotherapy of tuberculosis. V. Thiosemicarbazone and the latest compounds, Brit. J. Pharmacol., 1949, 4: 248.

ment temporarily interrupted. It was estimated by Heymer that about 10 per cent of patients will suffer gastrointestinal disturbances on a total daily dose of 2 to 4 mg. per Kg. body weight. Boehm and Brecke observed anorexia in 44 per cent of patients, and it was severe enough to require discontinuation of treatment in 8.6 per cent of patients (table 1). Their recommendations for dosage ranged from 0.05 to 0.2 Gm. per patient per day.

Vomiting was observed occasionally by other observers when larger doses were employed and Boehm and Brecke report vomiting in 17 per cent of their series of 245 patients.

Several of the physicians interviewed were using small doses (under 50 mg. per day) and these apparently caused very little gastrointestinal disturbance. It is probable that their therapeutic results were less striking when such doses were employed.

*Jaundice and fatty infiltration of the liver:* There is considerable confusion as to whether Conteben is toxic to the liver. Because of this uncertainty, a special meeting was held in July 1949 at Möln for the purpose of considering this problem. The meeting was attended by approximately twenty investigators and all reported that jaundice was a common condition among both treated and untreated patients, but usually occurred more frequently among those treated. It was postulated that this might be, at least in part, homologous serum jaundice transmitted by needles and syringes, for studies involving venipuncture were frequently carried out on patients under thiosemicarbazone treatment. Martini reported to us that he observed jaundice in 33 of 197 treated patients (17 per cent) and in 11 of 189 untreated patients (6 per cent), but he did not believe jaundice to be caused by thiosemicarbazone. (It so happened that the incidence of jaundice in both treated and untreated patients was considerably higher in one of his clinics than in the other).

Doctor Mueller, the pathologist of the Essen Hospital, had performed autopsies on 17 patients who had received Conteben and he told us that he had noted fatty infiltration and "reticulosis" but no necrosis, and he believed these changes to be reversible. Similar changes, but to a lesser degree, have been seen by him in patients dying without treatment.

Brecke and Boehm have observed the liver at laparotomy or peritoneoscopy in a few cases. Abnormal appearances attributable to treatment were noted several times and in three instances the liver was observed during treatment and again some time after the conclusion of treatment. In the latter instances the liver had returned to a normal appearance, confirming the opinion that the damage is reversible but genuine. Brecke told of two autopsies in patients dying after Conteben treatment and stated that there was but slight fatty infiltration of the liver. Interpretation of the relation of Conteben to hepatitis is further complicated by the fact that during the early experience with high doses hemolytic crisis with jaundice was observed.

At present, the problem of the relation of Conteben to hepatitis must remain an open question. It seems reasonable to assume, however, that the drug is capable of inducing hepatitis until evidence to the contrary is available.

*Agranulocytosis:* Eight instances of agranulocytosis among 2,000 patients who received Conteben were reported to us: Professor Klee, one; Doctor Heymer, two; Doctor Heim, one; Professor Kuhlmann, two; and Professor Heilmeyer, two. One of Heilmeyer's patients died of this complication but none of the other reactions were fatal. In both of Heilmeyer's cases and in several of the others, the patients had been receiving aminopyrine at the time of the appearance of agranulocytosis. Assuming that the over-all incidence of agranulocytosis is of this order (approximately 4 per cent per 1,000), the use of the drug would not be invalidated but careful observation of leukocyte counts would be a necessary precaution during treatment.

*Effects upon hematopoietic system,*[8] *serum proteins, and erythrocyte sedimentation rate:* Heilmeyer had observed one hemolytic crisis which he attributed to Conteben therapy. Pribilla and Koester of Essen (not seen by us but published in Deutsch med. Wchnschr. June 24, 1949 **74,** 795) reported 6 hemolytic reactions. Most of these patients received 0.5 Gm. daily, a dose now considered to be well within the toxic range.

With the doses now in use (.050 to 0.2 Gm. daily), hemolytic crises have not been observed elsewhere and must be considered to be a relatively rare complication. Heim described one leukemoid reaction which did not prove to be serious.

An unknown percentage of patients (apparently less than one-half) developed anemia of mild degree after receiving Conteben treatment. Except for the hemolytic crises mentioned above, the lowest concentration of hemoglobin noted during drug-induced anemia was "60 per cent." In response to a hypothetical question as to probable results of overdosage, Martini expressed the belief that "serious blood damage" might ensue.

Kuhlmann has utilized transfusions quite frequently but more to restore depleted serum proteins than for treatment of anemia. He stated that patients with initial anemia and hypoproteinemia do not respond to thiosemicarbazone therapy. He believes that serum albumin transports the drug in the blood stream, but did not give the evidence for this hypothesis.

There was great interest in the subject of serum proteins in tuberculosis and several centers are carrying out electrophoresis studies. They note an increase in gamma globulins as the patient's condition improves during Conteben therapy and as this fraction includes certain antibodies they regard the finding as a favorable one.

A strange and potentially deceiving effect of Conteben therapy has been observed repeatedly in determinations of the sedimentation rate of erythrocytes. Within a few days of the start of treatment there is usually an impressive decrease in sedimentation rate with high values returning to essentially normal levels. Heilmeyer has made a special study of this phenomenon, and has concluded that it is a nonspecific effect occurring in patients with and without tuberculosis. He believes, therefore, that the sedimentation rate loses its import as an index of improvement during Conteben therapy. Nevertheless, other investigators often stressed the decreased erythrocyte sedimentation rate as evidence of therapeutic effect.

*Central nervous system:* Heim has observed 2 cases of cerebral edema, with alleged autopsy proof of diagnosis (one patient died of hemorrhage, the other of intestinal perforation). It was not possible for us to determine with any certainty whether the alleged encephalopathy contributed to the death of the patients but it was assumed that it did not.

Kalkoff (not visited by writers) has reported (Beitr. z. Klin. Tuberk., 1948, 101: 395) two instances of fatal encephalopathy during therapy with TbI/698/E, a preparation which contains sulfathiazole. The doses used in both patients were unusually high, however, and consisted of as much as 750 mg. daily to an eight-year-old child and 1.0 Gm. to a 60-year-old adult. Other investigators using the standard dosage have not recognized any significant central nervous system symptoms or findings except for the rather high incidence of headache and dizziness reported by Boehm and Brecke (table 1).

Several times we inquired regarding evidence of peripheral neuritis and in no instance had such findings been observed.

*Renal toxicity:* Malluche reported mild albuminuria occasionally but neither he nor any other investigator regarded Conteben as a nephrotoxic drug. Heymer has treated 7

[8] Since this report was made a nonfatal case of thrombocytopenic purpura from TbI has been reported (Schmidt-Voight and Gensch: Tuberkulose-arzt, 1949, 10: 576).

patients who had amyloidosis with renal damage, and they tolerated the drug satisfactorily.

Several investigators were questioned as to the possibility of nitrogen retention or other evidence of impairment of renal function, and a negative answer was always obtained. Martini had observed renal function with special care in patients receiving Conteben and concluded that renal damage was no hazard.

*Skin rashes and conjunctivitis:* Exanthemata were observed by all investigators. Usually the eruption consisted of a toxic erythema or morbilliform rash, but occasionally urticarial or rarely petechial eruptions were described. Pribilla and Koester (see hemolytic anemia above) have reported the occurrence of one fatality during an allergic reaction to Conteben. The course of events in this case was similar to that observed during toxic reactions to sulfonamides.

TABLE 1

*Toxic Manifestations Observed in 245 Patients Treated with Conteben by Doctors Boehm and Brecke**

| | TOTAL | | SEVERE ENOUGH TO STOP TREATMENT | |
|---|---|---|---|---|
| | Number | Per cent | Number | Per cent |
| a. No toxicity | 94 | 38.37 | — | — |
| b. Toxic manifestations noted | 151 | 61.63 | 52 | 21.22 |
| 1. Anorexia | 107 | 43.67 | 21 | 8.57 |
| 2. Vomiting | 43 | 17.55 | 15 | 6.12 |
| 3. Headache | 24 | 9.79 | — | — |
| 4. Dizziness | 14 | 5.71 | — | — |
| 5. Kidney irritation | 15 | 6.12 | — | — |
| 6. Liver disturbance | 5 | 2.04 | 1 | 0.41 |
| 7. Icterus, jaundice | 5 | 2.04 | 5 | 2.04 |
| 8. Sensitization against egg albumin† | 5 | 2.04 | — | — |
| 9. Anemia | 5 | 2.04 | 3 | 1.22 |
| 10. Agranulocytosis (not total) | 1 | 0.41 | 1 | 0.41 |
| 11. Rash | 13 | 5.31 | 4 | 1.63 |
| 12. Conjunctivitis | 9 | 3.67 | — | — |
| 13. "Heartburn," colic, obstipation | 8 | 3.27 | — | — |

* Interpretations and conclusions are those of Doctors Boehm and Brecke.

† See text.

Conjunctivitis was also seen by nearly every observer, but only occasionally, and never did the reaction reach alarming proportions. It should be mentioned here that the earlier preparations of Conteben were combined with sulfathiazole (TbI/698/E) and from the records it was not always possible to exclude the participation of sulfathiazole in toxic reactions.

Heymer stated that 50 per cent of his patients noted itching of the hands but this was not noted by others and did not appear to be a significant symptom.

No instances of exfoliative dermatitis were reported to us.

Boehm believes that Conteben administration may lead to an increased sensitivity to cheese protein. It should be noted that all of his patients were women. Brecke, whose study is organized in a fashion comparable to Boehm's but whose patients are all men, has not been impressed by this phenomenon.

*Therapeutic Effectiveness*

The problem of the evaluation of any drug in the treatment of tuberculosis is difficult, but is particularly so when it is universally agreed that the drug is not sufficiently powerful to exert an impressive effect upon the course of miliary or meningeal tuberculosis. This is the case with Conteben and the problem is further complicated by the fact that a radical improvement in the nutritional status of the patients (notably the repatriated war prisoners) coincided with the period of drug-testing. Moreover, the supply of roentgenographic film in Western Germany has not been abundant and many of the patients in the Conteben study had to be examined by the use of paper film. Nevertheless, despite these handicaps, it was possible to arrive at certain conclusions on the basis of the evidence presented to the reviewers. This evidence is presented immediately below.

*Tuberculous meningitis and miliary tuberculosis:* Klee demonstrated one patient with proved tuberculous meningitis who received Conteben orally and "Tb.VI" intrathecally[9] from January through April 1949 and the disease apparently had been arrested. This was the only indication which was presented to us of a favorable effect of the thiosemicarbazone drugs on this form of tuberculosis. Other clinicians reported little or no effect of Conteben medication and regarded streptomycin as the treatment of choice for tuberculous meningitis. For obvious reasons they are not willing to withhold streptomycin from such patients when it can be obtained. Kuhlmann treated 3 patients with tuberculous meningitis with Conteben when he was unable to obtain streptomycin and all 3 died. He thought that their lives may have been prolonged for "a few weeks."

The situation with miliary tuberculosis was similar and we saw no instance of classical generalized hematogenous miliary tuberculosis with recovery unless streptomycin had been administered. Domagk stated that 3 cases of miliary tuberculosis had been cured and one such case was reviewed (Kuhlmann), but conclusive diagnostic evidence was not presented. It is not likely that further evidence on this point will be forthcoming for it is now the general practice in Germany to administer streptomycin immediately to all patients with meningeal or miliary tuberculosis.

*Laryngeal tuberculosis:* The effect of Conteben therapy on tuberculosis of the larynx was uniformly impressive and resembled the effects of streptomycin.

The pain and dysphagia of severe, ulcerative, tuberculous laryngitis was reported to disappear within a few days, hoarseness disappeared, and subsequently the lesions improved objectively over a period of several weeks. Complete healing of the lesions has been observed almost uniformly within a period of six to eight weeks. We talked with patients who described their dramatic improvement to us and these patients spoke with nearly normal voices.

Schaich urged local treatment with Conteben powder applied with a blower directly to the larynx. Since this drug is eventually swallowed, however, it was difficult to regard this as topical treatment alone.

The number of cases of tuberculosis of the larynx treated by the various observers must total nearly 200 and the favorable results were variously estimated from 90 to 100 per cent good to excellent. New lesions have appeared during treatment, however, but rarely after the first few weeks.

The results in these laryngeal cases constitute acceptable evidence that Conteben has a definite effect on tuberculosis.

*Tuberculous enteritis:* Tuberculous enteritis appeared to be unusually common among patients in German sanatoriums. Virtually all of the investigators we saw placed a great

[9] A soluble derivative of TbI.

emphasis on roentgenographic findings in both the diagnosis and the continued observation of patients with this form of tuberculosis. As a consequence, in the majority (possibly as many as two-thirds) of the patients who received Conteben for alleged intestinal tuberculosis, the diagnosis was based entirely on roentgenographic findings. For example, in Boehm's series of 42 cases of tuberculous enteritis, two-thirds were asymptomatic.

Kuhlmann was also particularly interested in intestinal tuberculosis, and estimated that he had treated 60 to 70 patients. Heymer has treated 30 to 40 patients and each of the other investigators has treated at least a few patients with intestinal tuberculosis, and often a considerable number. In these series also, the diagnosis was made solely by roentgenographic study in a large number of the cases. This point is emphasized because the reviewers believe that roentgenographic studies of the intestine are an unreliable index by which to evaluate the effectiveness of an antituberculous drug.

Every investigator was questioned directly and *each responded that 100 per cent of all patients with symptoms of intestinal tuberculosis obtained relief* with Conteben therapy. Diarrhea ceases within a few days usually and pain is quickly eased. Fever subsides within a few weeks at most and eventually roentgenologic evidence of healing is observed. Many clinical records demonstrating these findings were shown to the reviewers.

As tuberculous enteritis is such a grave complication of pulmonary tuberculosis and is usually refractory to all treatment except chemotherapy, we could not but accept this as evidence that Conteben has a clinically recognizable antituberculous activity. It is interesting to note that Conteben, like streptomycin and para-aminosalicylic acid, is peculiarly effective against tuberculous enteritis.

Brecke and Boehm described 4 patients whose tuberculous enteritis healed with cicatricial deformities producing intestinal obstruction and requiring resection. The resected bowel was examined microscopically and ulcerations were healed, but there were remnants of tuberculous infiltration in the submucosal zones. Malluche reported similar findings in one or more cases.

Exacerbations of symptoms of tuberculous enteritis have been observed after cessation of therapy and these have again responded to Conteben therapy. Prolonged treatment (perhaps six months) appears to be desirable in cases of tuberculous enteritis.

*Pulmonary tuberculosis:* It was obvious that the German investigators were plagued with the same difficulties in evaluating Conteben in pulmonary tuberculosis as had been faced by those of us who sought to evaluate sulfone drugs and streptomycin. Some patients recover remarkably without specific therapy, others are beyond all hope of any treatment. Between these extremes are many and mixed types of disease, and judgment is notoriously fallacious as to the true cause of observed improvement.

The number of patients treated in the institutions visited reaches an impressive total but, when this was compared to the bed capacity[10] of each hospital it was instantly obvious that a large percentage of patients must have received Conteben therapy. What is more disturbing is the fact that treatment was undertaken in the past two years during which time nutrition and medical care has improved in Germany to an impressive degree. Furthermore, this has been a period when considerable numbers of prisoners of war have been returning, especially from eastern Europe, often in deplorable physical condition, and have been receiving simultaneously and for the first time, good food, rest, good nursing care, and good medical supervision, as well as Conteben. The German physicians recognize

[10] We did not assemble figures of bed capacity, but the six sanatoriums were of moderate size for the main part (150 to 300 beds) and the four tuberculosis departments of general hospitals were of still more limited size.

this factor in most instances, but expressed the unqualified opinion that Conteben had played a significant part in the remarkable recovery of some of these patients.

Comparison of the course of the infection prior to treatment with that observed during treatment was emphasized strongly by many of the investigators as evidence of the effectiveness of the thiosemicarbazone. In our opinion there is a fundamental fallacy in this

TABLE 2

*Acute Forms of Pulmonary Tuberculosis Treated with Conteben by Doctors Boehm and Brecke**

| Evaluated | 64 cases = 100 per cent |
|---|---|
| *Not influenced* | *14 cases = 21.87 per cent* |
| 10 progressive cavernous tuberculosis | |
| 3 fresh disseminations | |
| 1 late miliary tuberculosis | |
| *Partially influenced* | *12 cases = 18.75 per cent* |
| 11 older exudative tuberculosis with strong productive admixture | |
| 1 fresh dissemination | |
| *Decidedly influenced* | *38 cases = 59.38 per cent* |
| 17 fresh exudative cavernous tuberculosis | |
| 19 fresh disseminations or extensions | |
| 1 fresh miliary tuberculosis | |
| 1 primary tuberculosis | |

*Summary*

| | NUMBER OF PATIENTS |
|---|---|
| Reduction of recently disseminated or progressive lesions | 19 |
| Reduction of other shadows | 16 |
| Shrinkage of cavities | 7 |
| Disappearance of the bacilli in the sputum culture | 12 |
| Temperature reduction | 28 |
| Improvement in sedimentation rate | 27 |
| Collapse therapy made possible by previous chemotherapy | 7 |

* Interpretations and conclusions are those of Doctors Boehm and Brecke.

reasoning, however, when studies in a disease like tuberculosis are made during a period of rapidly ascending quality of general medical care and nutrition.

Brecke and Boehm attempted to select a control series of patients who received no specific therapy and told us that 25 per cent of these improved spontaneously. A similar but not contemporary series of treated patients contained about 60 per cent who improved (tables 1 and 2). Martini and his associates observed about 50 per cent of "excellent" to "probable" therapeutic results (table 4).

With the above reservations in mind it can be stated that the reviewers were shown a

large number of cases in which an impressive degree of roentgenographic clearing of pulmonary lesions had occurred during relatively prolonged Conteben therapy, i.e., four to six or nine months. There was no question concerning the fact that the patients had attained excellent results but, for the reasons mentioned, it was not possible to relate

TABLE 3

*Treatment of Chronic Forms of Pulmonary Tuberculosis with Conteben by Doctors Brecke and Boehm**

| Evaluated | 57 cases = 100 per cent |
|---|---|
| *Not influenced* | *38 cases = 66.66 per cent* |
| 24 productive fibrous, cavernous phthisis | |
| 6 productive infiltrative phthisis | |
| 5 persistent cavities after thoracoplasty | |
| 1 chronic miliary tuberculosis | |
| 2 caseous bronchopneumonic forms | |
| *Partly influenced* | *16 cases = 28.08 per cent* |
| 11 productive cavernous or ulcerous types | |
| 4 productive infiltrative types | |
| 1 persistent cavity after thoracoplasty | |
| *Decided influence* | *3 cases = 5.26 per cent* |

* Interpretations and conclusions are those of Doctors Brecke and Boehm.

TABLE 4

*Summary of 181 Cases of Pulmonary Tuberculosis Treated with Conteben by Professor Martini (Chief of Medicine, University of Bonn) Between September 1947 and September 1949**

I. 87 cases from which no conclusions were drawn because of:
  (a) Treatment too brief (29 cases)
  (b) Criteria for evaluation inadequate (13 cases)
  (c) Other therapy included: collapse, streptomycin, and so forth (16 cases)
  (d) Observation period before treatment too brief (19 cases)
  (e) Tendency to improve noted before treatment started (10 cases)

II. 94 cases evaluated
  (a) Therapeutic effects observed (72 cases)
    (1) Striking, convincing evidence (29 cases)
    (2) Probably evidence of good result (18 cases)
    } Total 47 cases or 50% of 94 cases.
    (3) Clinical improvement, but no other evidence of good result (X-rays, and so forth, unchanged) (33 cases)
    (4) Transitory improvement only (22 cases)
  (b) No therapeutic effect observed (21 cases)
  (c) Disease progressed despite treatment (1 case)

* Interpretations and conclusions are by Professor Martini.

the results with absolute certainty to the administration of Conteben. About the most that can be said is that these particular types of observations were "suggestive" of some drug effect.

The reviewers repeatedly were shown films of patients which demonstrated reduction

in size of cavities, leading us to suspect a favorable effect of the drug upon endobronchial tuberculosis, although bronchoscopy was rarely performed. Furthermore, the tomographic films demonstrated were not always comparable, as depth measurements were obviously inaccurate in at least a few instances. (This was judged by appearance of the thoracic cage and other shadows in serial films.)

Malluche was exceedingly enthusiastic about combining local intracavitary treatment (Conteben suspended in glycerin) with the Monaldi drainage maneuver. Without such cavernostomy, he has seen little or no favorable effect of the drug on giant cavities. He has applied such combined treatment to 48 cases, mostly during 1949, and unquestionably the early results are superior to any treatment previously observed by us for giant cavities. Whether these cavities will reopen remains to be seen; certainly this has occurred frequently when the Monaldi procedure is used alone. He reported that the cavernostomy fistulas uniformly close within a few days after removal of the tube, thus obviating one of the most serious handicaps to the Monaldi procedure. He obtained proof of cavity closure by roentgenographic examinations after instillation of iodized oil before removing the drainage tube. Doctor Malluche is very intense, enthusiastic, and undoubtedly skillful, and it is possible that less expert investigators might not be able to reproduce his striking results with equal uniformity.

German physicians whom we interviewed agreed that Conteben treatment, like streptomycin treatment, is but one phase of medical treatment in tuberculosis. They often expressed the belief that Conteben could be used more frequently than streptomycin, and it appeared that they were using it almost routinely in some institutions.

Conteben, like streptomycin, has apparently permitted physicians to be more radical in their employment of collapse procedures, especially pneumothorax. Pulmonary resection for tuberculosis is not widely used in Germany, it appeared to us, for no one we interviewed had attempted the procedure, and it remains to be seen if Conteben offers adequate protection against the tuberculous complications of lobectomy and pneumonectomy.

The general consensus of physicians interviewed was that Conteben, like streptomycin, is most likely to affect favorably fresh-exudative, nondestructive types of pulmonary tuberculosis. *It is also a general opinion that Conteben is neither as dependable nor as rapid in its action on pulmonary lesions as is streptomycin.* Several expressed the opinion that Conteben should first be tried and, if unsuccessful, streptomycin or para-aminosalicylic acid should be added. The economic factor also entered into this reasoning, for both streptomycin and PAS require dollar exchange and are expensive, while Conteben is said to be a much cheaper drug in addition to its being a local product in Germany.

Only a little evidence was produced to indicate that thiosemicarbazone-resistant tubercle bacilli may eventually appear in clinical infections (5 cases of Brecke and Boehm), and no bacteriologic studies of sensitivity were made.

No studies have been made to determine if Conteben administered with streptomycin will delay the emergence of streptomycin-resistant bacilli. On theoretical grounds we believe that such might prove to be the case. If such a study showed no such effect, however, it would tend to shake our faith in the value of Conteben in pulmonary tuberculosis.

*Tuberculous empyema:* Conteben has developed a good reputation in Germany as a remedy for tuberculous empyema when introduced as aqueous suspension directly into the infected pleural space. Most of the cases presented to us were instances of empyema developing after closed intrapleural pneumonolysis by cautery, and treatment consisted not only of local Conteben therapy, but also pleural lavage, azochloramide, and oral

Conteben treatment. When bronchopleural fistulas were present (cavity "blow out") the results were very poor, as is true with all other therapeutic approaches to this situation.

Specific recommendations made by Malluche were that 0.1 to 0.3 Gm. of Conteben in an aqueous suspension (10 to 20 per cent) be instilled every few days into the infected pleural space by needle puncture. Kuhlmann also presented several cases, utilizing similar methods and also employing "Tb. VI" intrapleurally in some cases. (Domagk told us that TbI (Conteben) and "Tb. VI" are essentially the same drug except that the former is very insoluble in water and the latter is soluble, making it more suitable for local and parenteral use.)

Since streptomycin has proved to be of so little value in treatment of tuberculous empyema, this may be an important use for Conteben treatment if these results can be confirmed.

*Genitourinary tract tuberculosis:* Originally it had been planned to visit the clinic of Professor Boshamer, a urologist who has had extensive experience with treatment of tuberculosis of the kidneys and bladder, but he was out of town and his results were summarized for us by Doctor Bunge of the Bayer Company. Boshamer has treated about 50 cases of genitourinary tract tuberculosis with alleged excellent results. Bladder ulcerations and the resultant symptoms improved rapidly, tubercle bacilli in the urine were reduced in number, but were rarely eradicated, and renal lesions improved but little pyelographically.

Kuhlmann described 4 cases of renal tuberculosis treated with good results and he said that he had treated "four or five" patients with tuberculous epididymitis with excellent results. One of these patients was demonstrated to us, but open draining sinuses were still present and the result would not compare favorably with that which we are accustomed to see following streptomycin therapy.

Klee, Heymer, Heim, Brecke, and Boehm also mentioned small but favorable experiences with Conteben therapy of genitourinary tract tuberculosis (table 5).

Domagk demonstrated a prostate obtained at autopsy which showed what he believed to be remarkable healing of tuberculous prostatitis.

It should be emphasized that because of the nature of this type of tuberculosis and the relatively few cases treated by each investigator, the above statements concerning Conteben in genitourinary tuberculosis have really no more weight as evidence than hearsay.

The treatment of genitourinary tract tuberculosis requires that the antibacterial action of the drug be long continued, and we believe that duration of action may be more important than intensity of action. Hence Conteben might prove to be especially adaptable to the treatment of this condition.

*Tuberculous sinuses, fistulas, and abscesses:* Several observers have treated small series of patients with draining sinuses and fistulas with or without localized abscess formation. While all agreed that the drug has a favorable effect, none were able to obtain results which compare favorably with those obtained in America with streptomycin therapy (table 5). Results were slower in appearing, less convincing, and perhaps less permanent than with streptomycin.

Malluche had instilled aqueous suspensions of Conteben directly into cold abscesses, especially those associated with bone tuberculosis, with results which he regarded as excellent. He presented films and detailed charts of 2 such patients to us: tuberculosis of ankle bone, 1 case; tuberculosis of lumbar vertebrae, 1 case. The tissues apparently tol-

erate the drug quite well, and perhaps the insolubility of the drug is a desirable attribute, as a depot of the antibacterial agent is presumably established at the site of the disease process.

### *Conclusions*

The thiosemicarbazone, Conteben, has been utilized in Germany on a vast scale during the past two years and this development has scarcely reached the attention of the medical profession in America.

TABLE 5

*Treatment of Extrapulmonary Tuberculosis by Doctors Brecke and Boehm**

| | TOTAL | DECIDED EFFECT | TRANSITORY EFFECT | NO EFFECT |
|---|---|---|---|---|
| 1. Lymphadenitis and fistulas | 41 | 24 | 8 | 9 |
| 2. Empyema | 7 | 3 | 2 | 2 |
| 3. Mouth, throat, larynx | 19 | 16 | 1 | 2 |
| 4. Bronchus | 14 | 12 | 1 | 1 |
| 5. Tuberculous enteritis† | 42 | 28 | 12 | 2 |
| 6. Bladder | 2 | 2 | — | — |
| 7. Endometritis | 1 | 1 | — | — |
| 8. Poncet syndrome | 3 | — | 3 | — |
| | 129 = 100 per cent | 86 = 66.7 per cent | 27 = 20.9 per cent | 16 = 12.4 per cent |

* Interpretations and conclusions are those of Doctors Brecke and Boehm.

† Two-thirds of patients with tuberculous enteritis had roentgenographic findings but no symptoms.

Conteben is not a sufficiently powerful antituberculous drug to exert a significant influence on most instances of miliary or meningeal tuberculosis.

Other types of clinical tuberculosis which have been proved to be most responsive to other antituberculous drugs in America and elsewhere appear to have responded to Conteben therapy in Germany. Most impressive have been the results observed in treatment of the more superficial but very serious types of mucous membrane complications of extensive pulmonary tuberculosis, especially tuberculous laryngitis and tuberculous enteritis.

Pulmonary tuberculosis, treated before irreversible pathologic changes have developed, probably responds to Conteben therapy but doubt remains as to whether this is the preferable drug when other drugs are available, notably streptomycin.

In most forms of extrapulmonary tuberculosis there is some evidence, often incomplete and sometimes confusing, which suggests that Conteben, alone or in combination with other antituberculous drugs, may prove to be a valuable adjunct in treatment.

Conteben has a potential toxicity which would seem to be definitely greater than is the case with either streptomycin or para-aminosalicylic acid. Nevertheless, on the basis of the present evidence there is every reason to believe that with proper caution the drug can be administered for long periods of time without undue risk.

A crude approximation of the current situation can be made by the statement that Conteben appears to have: antituberculous activity of the same general order as para-aminosalicylic acid; and a potential toxicity somewhat like the arsenicals used in the treatment of syphilis.

If no superior antituberculous agents are developed, a drug with these apparent degrees of antituberculous activity and toxicity would be an important addition to the currently available antimicrobial agents. It is virtually certain, however, that Conteben would not replace streptomycin but would be used together with streptomycin in the treatment of tuberculosis.

*Recommendations*

The data regarding Conteben which have been assembled in Germany are sufficiently promising so that the drug can no longer be ignored in America. These data fully justify a prompt and thorough series of experimental and clinical trials in the United States.

Experimental studies should be directed toward: (a) comparison between Conteben and other antituberculous drugs in experimental animals; (b) *in vivo* and *in vitro* studies to determine if tubercle bacilli resistant to thiosemicarbazone will emerge; (c) pharmacologic studies to evaluate the toxic properties of Conteben in animals; (d) studies to determine the absorption, distribution, and excretion of this drug in animals and in man and (e) experimental trial of other thiosemicarbazones.

Clinical studies should be directed toward: (a) an attempt to determine in what circumstances Conteben may be the drug of choice, and when it is to be used as an auxiliary to other available antituberculous drugs; (b) developing much more objective and more complete studies regarding toxicity of Conteben to human beings when given in highest tolerated doses; (c) determination if Conteben will delay the emergence of streptomycin-resistant tubercle bacilli when administered concurrently with streptomycin.

H. Corwin Hinshaw
Walsh McDermott

September 29, 1949

# *Letters to the Editors*

## PULMONARY COCCIDIOIDOMYCOSIS

*To the Editors of the American Review of Tuberculosis:*

Recent years have seen a rising interest in pulmonary coccidioidomycosis. As a result of the occurrence of the infection in army personnel who were stationed in the endemic areas, we are now observing the residual pulmonary lesions in veterans. Occasional non-veteran cases are also being seen in individuals who resided in or traveled through the Southwest for business, vacation, or health reasons.

Pulmonary cavitation is a frequent manifestation of residual coccidioidomycosis. These cavities may superficially resemble tuberculous cavities. Unlike tuberculosis, the coccidioidal cavity is generally benign, except for the rare case of severe hemoptysis. Recent follow-up studies of these cavities, continuing for seven years in some instances, indicate that, except for fluctuation in cavity size or shape, complications are the exception. Bronchogenic spread of disease does not occur, and lymphohematogenous dissemination from a cavity is dubious.

The danger of transmitted infection to other individuals through intimate family contacts, for instance, has not been borne out by the available clinical evidence. In general then, the behavior of the coccidioidal cavity is totally unlike the tuberculous cavity, and clinical experience suggests a conservative approach to the question of therapy. Indeed, it would appear that no therapy whatever is indicated, except in the case of recurrent severe hemoptysis.

A large number of veterans with coccidioidal cavities now residing in New York City have been under observation since their discharge from military service. They are all asymptomatic, are engaged in normal activities, and are working at various occupations without any handicaps whatever.

It is somewhat disturbing, therefore, to note the recent papers describing pulmonary resection for cases of coccidioidal cavities. Since August 1949, three such reports have appeared in the Journal of Thoracic Surgery alone. In some of these cases, the indications for surgery were loss of weight, malaise, danger of dissemination, and fear of transmitted infection. In the light of the experience of C. E. Smith (M. Clin. North America, 1943, *27*, 790), W. A. Winn (Arch. Int. Med., 1941, *68*, 179), myself and others (Bass, Schomer, & Berke: Arch. Int. Med., 1948, *82*, 519; Am. Rev. Tuberc., 1949, *59*, 632) who have had occasion to observe the benign nature of the coccidioidal cavity, these indications do not appear to be valid. It is to be hoped that the medical chest specialist who has occasion to see a case of coccidioidal cavitation will exert a braking influence on his thoracic surgical colleagues.

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November 7, 1949

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# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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## CLINICAL STUDIES, TUBERCULOSIS

**Cutaneous Primary Complex.**—In 4 cases of primary tuberculosis of the skin diagnosis was based on conversion of the tuberculin test from negative to positive, on the absence of clinical and roentgenological signs of prior tuberculosis infection, and on morphological changes characterized by ulceration together with enlargement of the regional lymph glands. In 2 of the 4 cases the incubation period was established as being between ten days and three weeks.— *Le complexe primaire cutané dans le cadre de la tuberculose primaire de l'organisme, G. Piotet, Schweiz. Ztschr. Tuberk., 1994, 6: 69.—(E. Dunner)*

**Lower Lobe Tuberculosis.**—A series of chest roentgenograms were reviewed for cavitation in the apex (dorsal segment) of a lower lobe. Lesions were accepted only if they were localized by a lateral view, tomography, or bronchography. Only 54 cases met these criteria. The clinical characteristics were similar to those in a random series of cavitary lesions except that the lower lobe lesions were chiefly on the right and pain was a more frequent symptom. The cases were studied from the viewpoint of cavity closure as judged by strict criteria. It was found that in 33 cases (60 per cent) the cavity was closed by artificial pneumothorax with or without supplementary pneumonolysis or phrenic paralysis. Since pneumothorax was tried in 44 cases, it was successful in 75 per cent. The results were doubtful in 6 cases; in 6 others no free space was obtainable. The incidence of pleural effusion and empyema was no higher than in the random series, and the results were about as good. It is felt that artificial pneumothorax is the initial treatment of choice supplemented, if necessary, by a pneumonolysis or phrenic paralysis or both.—*Tuberculous cavities in the apex of the lower lobe, J. Crofton, Thorax, June, 1949, 4: 96.—(A. G. Cohen)*

**Pregnancy in Pulmonary Tuberculosis.**—A review of 118 cases of tuberculosis in pregnancy showed that patients often seem improved until delivery, and that the postpartum exacerbation arises from the greatly increased intrapulmonary pressure developed by straining in the second stage. The best solution to this problem seems to be Caeserian section; the next best may be caudal or spinal analgesia with low forceps extraction. Therapeutic abortion is seldom justified and should never be employed after the third month as it is then more dangerous than proper delivery.—*Tuberculosis and pregnancy, H. Johnson, J. Burch, D. Bayer, & G McClellan, J. Thoracic Surg., October, 1948, 17: 646.—(R. E. MacQuigg)*

**Prognosis in Cavitary Tuberculosis.**—Positive sputum is regarded as the criterion for the presence of a cavity. The fate of 1,233 unselected positive sputum cases after twenty years was investigated. There was found to have been improvement in the three- and five-year survival period from 1934 to 1936 onward. There was also improvement in the eight-year survival period during 1937 to 1939. This improvement was due to the various advances in treatment and care that have taken place. There was nonsignificant improvement in the ten-year survival rate. These studies indicate that the greatest care must be

used in evaluating the apparent efficacy of any new type of treatment.—*The fate of the tuberculous cavity, B. Mann, Tubercle, June, 1948, 29: 131.—(A.G. Cohen)*

**Tuberculous Pleural Effusion.**—Primary serous pleural effusion is a disease of young people. In males, the predominant age is sixteen years, in females seventeen to twenty-two. The age incidence is lower in warmer climates because of earlier puberty. The ratio of incidence between the sexes is approximately the same as the sex ratio in the civilian population. The right side is affected in 55 per cent of patients. Stress of work and "weak chest" are unlikely precipitating factors. The incidence of chest pain is high. There is often paralysis of diaphragmatic motion after the fluid has absorbed. The white blood count is normal. There is strong evidence for a tuberculous etiology based on contact history, development of tuberculous complications, and symptomatology. In 14 cases tested, special culture methods revealed tubercle bacilli in every case. There is no difference in the behavior of the effusion because of the presence or absence of involvement of the pulmonary parenchyma. The pathogenesis is not known; the favored theory is that it results from a spread from a small primary pulmonary focus. Allergy is an important factor.—*Primary serous pleural effusion, A. F. F. Eberle, Tubercle, July, 1949, 30: 146.—(A. G. Cohen)*

**Schizophrenia and Tuberculosis.**—The occurrence of tuberculosis among 1,647 psychotic patients was studied in Stockholm. During July and August, 1939, chest roentgenograms and tuberculin tests were made on the group. Following this, the patients' temperatures were taken regularly and note was made of variations in their weight and blood sedimentation rates. The sputum and gastric contents were examined repeatedly for tubercle bacilli. Of all the patients, 5.3 per cent were found to have presumably active pulmonary tuberculosis, 6.1 per cent inactive pulmonary tuberculosis, and 12.1 per cent inactive tuberculosis in calcified areas. Among 1,026 schizophrenics, 68 (6.6 per cent) were found to have active pulmonary tuberculosis and 57 (5.6 per cent), arrested tuberculosis. In the catatonic subgroup the percentages were higher, 49 (10 per cent) of 489 catatonics having active and 30 (6.1 per cent), inactive or arrested tuberculosis. The hebephrenic and paraphrenic catatonics showed lower percentages, as did patients with other types of psychosis. Catatonic episodes generally were marked by considerable weight loss during which, in several cases, the development of pulmonary tuberculosis was noted. These weight losses also occurred in catatonic patients who did not develop tuberculosis, and may depend on a profound somatic disturbance accompanying the catatonic state. During this state resistance to tuberculosis may be lessened.—*Schizophrénie et tuberculose, C.-H. Alström, C. Gentz & K. Lindblom, Le Poumon, March-April, 1949, 5: 97.—(A. T. Laird)*

**Spontaneous Pneumothorax.**—One hundred consecutive cases of spontaneous pneumothorax were studied. Of these, 64 were known to have underlying pulmonary disease. In 20 per cent, there was a history of unusual exertion prior to the episode; in 80 per cent, it occurred during ordinary activity. Tuberculosis was noted in 38 cases, emphysema in 5, bronchiectasis in 5, and empyema, asthma, abscess, carcinoma, pneumonia and infarct each in a few. The great majority of the cases were in men; the average age was 27 years. In 3 patients there were multiple recurrences; one other subsequently developed spontaneous mediastinal emphysema and another developed tuberculosis after 4 recurrences. Aspiration of air was necessary in only 3 cases; in the others bed rest sufficed. In patients over 45 years of age, the appearance of spontaneous pneumothorax should arouse suspicion of underlying carcinoma.—*Spontaneous pneumothorax, R. M. Myerson, New England J. Med., April 1, 1948, 238: 461.—(A. G. Cohen)*

**Tuberculous Splenomegaly.**—A case is described of a 51-year-old Negro male who de-

veloped progressive thrombocytopenic purpura and died. At necropsy, tuberculosis of the spleen and the bone marrow was found. There are only a few recorded cases of purpura complicating tuberculosis of the spleen.—*Thrombocytopenic purpura associated with tuberculous splenomegaly and tuberculosis of the bone marrow, B. A. Gouley, N. Blumberg & R. J. Grayson, N. England J. Med., July 28, 1949, 241: 147.*—(*A. G. Cohen*)

**Caseating Pyelitis.**—Caseating pyelitis is a specific form of tuberculosis of the kidneys characterized by uniform caseation of the mucous membranes of the pelvis of one or both kidneys without massive destruction of the kidney parenchyma. In the same manner, the mucous membranes of the ureters, the bladder, and the seminal vesicles may undergo massive necrosis. Pathogenetically, pyelitis caseosa belongs to the group of early hematogenous metastases in a late primary tuberculosis infection. Biologically, it belongs to the Arthus phenomenon. The prognosis is grave. Streptomycin therapy is indicated, whereas operative intervention must be deferred until after stabilization of the tuberculous infection (Authors' Summary).—*Pyelitis caseosa, eine Frühform der exsudativen Nierentuberkulose, H. U. Gloor & E. Uehlinger, Schweiz. Ztschr. Tuberk., 1949, 6: 137.*—(*E. Dunner*)

**Antihistaminic Drugs for Tuberculosis.**—A series of 30 patients with active pulmonary tuberculosis was treated with various antihistaminic drugs in dosage of 300 to 400 mg. per day as tolerated. No significant changes were observed in the urine, erythrocyte sedimentation rate, or differential leukocyte count. A moderate increase in pulse rate was almost always noted after institution of therapy; dizziness and nausea occurred on large doses. Patients with tuberculous pneumonia and other acute exudative lesions seemed to show the greatest improvement. Serial tuberculin skin tests diminished in intensity while antihistaminic drugs were taken, but became positive again four to six weeks after stopping the drugs. Although skin sensitivity is not necessarily a measure of hypersensitivity existing in other tissues, it would appear that clinical improvement roughly paralleled suppression of the Mantoux reaction. Combined administration of antihistaminic drugs to suppress the allergic components of tuberculosis, and streptomycin to suppress the growth of the bacilli, may be very effective treatment.—*The use of antihistaminic drugs in human tuberculosis, A. R. Judd & A. R. Henderson, Ann. Allergy, May-June, 1949, 7: 306.*—(*B. Hyde*)

**Closed Intrapelural Pneumonolysis.**—In a series of 1,000 consecutive cases of closed intrapleural pneumonolysis, 27.6 per cent of the patients developed fluid which did not rise as high as the dome of the diaphragm. Tuberculous empyema appeared in 0.5 per cent within two months of surgery, and ultimately in 5.3 per cent. In this group are included all patients with turbid fluid requiring several aspirations. Pneumonolysis was partial in 42.3 per cent of the patients, complete in 49.8 per cent, and in 19 per cent was classified as a failure. Pneumothorax was prematurely lost in 32.8 per cent. Two postoperative deaths were attributed to the operation; 10 deaths were due to later complications attributable to the operation. Wider experience is leading to greater conservatism. Pneumonolysis is rarely justifiable in the presence of large cavities. It is contraindicated by peripheral cavities surrounded by dense adhesions, by tuberculous empyema or acute febrile pleurisy with effusion, by extensive progressive parenchymal disease, and by extensive adhesions. Enucleation of a broadly adherent lung by extrapleural dissection seems undesirable. The use of a single cannula (O'Brien) modification of the Cutler thoracoscope is recommended, with a high frequency spark gap.—*Closed intrapleural pneumonolysis, J. Day, P. Chapman, & E. O'Brien, J. Thoracic Surg., August, 1948, 17: 537.*—(*R. E. MacQuigg*)

**Extrapleural Pneumothorax.**—A late follow-up of 82 cases of extrapleural pneumothorax showed that 22 patients had died. Of the 67 extrapleural pneumothoraces in the 60 living

patients, 32 were maintained by air and 91 by oleothorax. Four had been re-expanded and 5 had persistent fluid usually containing tubercle bacilli. Of the 82 patients, 7 required further surgery, 5 having thoracoplasty and 2 pneumonectomy. The late results are considered satisfactory but the procedure has limited usefulness because of the difficult and prolonged care required. The procedure should usually be reserved for young, growing individuals who might be deformed by thoracoplasty. A small group of adults, in whom deformity would interfere with their vocation, also may be considered candidates.—*Extrapleural pneumothorax, H. Sullivan, J. Thoracic Surg., February, 1948, 17: 38.—(R. E. MacQuigg)*

**Extrapleural Pneumonolysis.**—Lateral thoracic branches of the internal mammary artery occur in approximately 50 per cent of individuals. These vessels course over the inner aspect of the upper and anterolateral aspect of the chest wall. They may be damaged when giving refills after an extrapleural pneumonolysis, resulting in serious hemorrhage into the extrapleural space. Moderate or massive hemorrhage occurs in 5 to 20 per cent of cases and may result in collapse of the patient or, more remotely, delayed infection or gradual obliteration of the space. When discovered at operation, the vessels should be ligated or coagulated with diathermy and, in addition, refills should at first be given from the back.—*Hemorrhage after extrapleural pneumonolysis, W. P. Cleland, Thorax, June, 1948, 3: 127.—(A. G. Cohen)*

**Collapse for Bilateral Tuberculosis.**—In a group of thoracoplasty cases, 11.2 per cent received contralateral pneumothorax. These were divided into three groups, according to the postoperative results. Group A, comprising those with negative sputum, totaled 14 cases, or 48.25 per cent. In all cases the lesions were arrested or quiescent. In group B, with positive sputum, there were 10 cases or 34.5 per cent. The lesions were stationary or improving in 5 and extending in 5. Group C contained 5 cases or 17.25 per cent; these were all dead. The initial prognosis in this type of case, requiring thoracoplasty in the presence of an active contralateral lesion, is poor. The pneumothorax must be managed with the greatest care. A marginal pneumothorax should be maintained and an attempt should be made to keep the lung at a constant distance from the chest wall. Three of 7 relapses and 2 of 5 deaths resulted directly from premature abandonment of the pneumothorax. The optimum time for such abandonment is debatable. The author believes that collapse should be maintained as long as possible.—*Bilateral active pulmonary tuberculosis treated with artificial pneumothorax and thoracoplasty, G. P. Maher-Loughann, Tubercle, May, 1948, 29: 101.—(A. G. Cohen)*

**Postpneumothorax Decortication.**—Lungs which cannot be expanded after pneumothorax because of extensive parenchymal destruction, fibrosis, or bronchostenosis are unsuitable for decortication. When the lung is bound to the chest wall by a thick visceral peel, decortication may allow re-expansion. This peel does not always arise from inflammation of the pleura itself. If the encasing plaque is found to be intimately adherent to the lung and adjacent to the old focus, it is left as a button on the lung. Of 5 cases, decortication was successful in 4; in one it failed because of internal fibrosis. The longest follow-up period was eighteen months.—*Decortication of the nonexpandable postpneumothorax tuberculous lung, D. A. Milvihill & R. Klopstock, J. Thoracic Surg., December, 1948, 17: 728.—(R. E. MacQuigg)*

**Resection for Pulmonary Tuberculosis.**—The authors report a series of 78 resections for pulmonary tuberculosis of which 23 were accidental and 55 deliberate. The accidental resections were performed for the mistaken diagnosis of bronchiectasis or carcinoma; altogether 462 operations were performed for these conditions. When tourniquet lobectomy was performed, there were frequent complications, chiefly pleural infection and bronchogenic spread. These have been eliminated

almost entirely by hilar dissection and individual ligation. In 15 of the cases, the preoperative diagnosis was bronchiectasis. Many had exhaustive sputum studies. There were 12 lobectomies and 3 pneumonectomies. Three of these patients died with a tuberculous spread. The preoperative diagnosis was carcinoma in 7 cases; there were 3 deaths. The remaining case was undiagnosed but had severe hemoptysis; the patient recovered. Of the 55 cases of known tuberculosis for which resection was performed, there were 15 cases of tuberculoma. Ten lobectomies and 5 segmental resections were done; recovery was rapid in all. There were 25 cases of persistent cavities not closed by other means and not suitable for thoracoplasty. The cavities were mostly in the apex of the lower lobe and bronchial lesions were often present. The choice of lobectomy or pneumonectomy must be decided in the operating room. Resection was rarely done for an upper lobe cavity unless there was bronchiectasis or multiple cavitation. There were 13 lobectomies and 6 pneumonectomies with one death. There were 3 cases of thoracoplasty failure. Resection is preferred to revision. There were 2 upper lobectomies and one pneumonectomy. All 3 developed pleural fistulae with spread and death. There were 9 cases of bronchial stricture with secondary suppuration; there was one death. There were 5 cases of destroyed lung which was unilateral. Streptomycin was available for only one-third of the operations. The head-down, face-down position is used. The operation finally may include a pleurectomy. It is not always possible to do a lobectomy because of obliterated fissures. Following lower lobectomy, a phrenicotomy is done to eliminate the dead space; following upper lobectomy, pneumoperitoneum also is given until the space is filled. After pneumonectomy a small upper thoracoplasty is done.—*Excision of the lung for pulmonary tuberculosis, T. H. Sellors & M. D. Hickey, Thorax, June, 1949, 4: 82.*—(*A. G. Cohen*)

**Resection for Tuberculosis.**—Brown presents 11 cases of pneumonectomy and 7 of lobectomy performed on patients for whom no other surgical procedure seemed to offer hope of success. Streptomycin was utilized during the immediate postoperative period to minimize the chances of spread. The following are indications of pulmonary resection in tuberculosis patients: (*1*) high grade bronchial stenosis, with or without associated suppurative disease; (*2*) tuberculoma; (*3*) cavity persisting after thoracoplasty; (*4*) lower lobe cavities which have not closed by collapse procedures; and (*5*) massive acute unilobar or unilateral tuberculosis in patients who deteriorate rapidly despite bed rest and streptomycin.—*Resection of lung for pulmonary tuberculosis, C. J. Brown, M. J. Australia, February, 1949, 1: 185.*—(*E. A. Rouff*)

**Pneumonectomy.**—One of the chief complications of pneumonectomy is infection of the space previously occupied by the lung which has been removed (the gap). Various methods of obliterating the gap, including thoracoplasty, have not been successful. In the case described pneumoperitoneum was combined with Monaldi suction applied to the gap. The Monaldi phase must await closure of the bronchial fistula. With this method, the gap was obliterated in a few months.—*Closing the pneumonectomy gap, G. S. Eddy, Lancet, June 12, 1948, 1: 905.*—(*A. G. Cohen*)

**Autogenous Bone Pegs in Ribs.**—Unless the cut rib ends are accurately approximated after thoracotomy, they will override, producing deformity, painful movement of the rib ends, or excessive callus. In a series of 50 patients the posterolateral intercostal incision was used. The cut ends of the ribs were locked together for closure by pegging their cavities with 3 cm. cortical bone pegs obtained from the inferior border of an adjacent rib. In 2 of these patients there was fracture of one peg on the first postoperative day, but a pain-free stable thorax was obtained.—*Medullary pegging in thoractomy incisions, K. P. Klassen, J. Thoracic Surg., February, 1949, 18: 90.*—(*R. E. MacQuigg*).

**Rib Fracture after Thoracoplasty.**—In 208 consecutive cases of thoracoplasty, postoperative fractures of the opposite first rib were discovered in 6 instances and of the first and second ribs in 2. All but one of the first rib fractures were in the middle third as were both of the second rib fractures. The fractures may result from prolonged muscular contraction in the area of greatest muscular stress and where the bone is thinnest. Clinically no symptoms were observed except by one patient who noted slight pain in the upper chest, and no therapy was necessary.—*Contralateral fracture of first and second ribs following thoracoplasty, A. Guggenheim & B. Cohn, J. Thoracic Surg., June, 1948, 17: 866.*—(*R. E. MacQuigg*)

**Early Roentgen Recognition of Lower-lobe Tuberculosis.**—Pulmonary tuberculosis originating in the lower lobe is generally considered uncommon because (*1*) most cases are discovered late after spread to other regions of the lungs has occurred, and (*2*) the midlung or "perihilar" infiltration is not recognized as lying in the upper portion of the lower lobe. If the disease were discovered earlier and a film taken in the lateral position, the reported incidence would be markedly increased. The most frequent site of the early lower-lobe lesion is in the apex or subapex of the lobe. In the postero-anterior view this produces characteristic, rather soft, transverse lines of infiltration extending from the hilus toward the periphery or limited to the middle or peripheral portion of the lung at the level of the hilus. The transverse position of these lines, as well as their beaded or finely nodular appearance, distinguish them from normal bronchovascular markings. In the lateral view, when the lesion is in the lower-lobe apex, the infiltration is well posterior near the chest wall. It appears lower or more anterior when in the subapical portion. Diagnosis should be made in this early stage before massive consolidation, cavitation, and spread have occurred.—*Early roentgen recognition of lower-lobe tuberculosis, H. W. Ostrum & W. Serber, Radiology, July, 1949, 53: 42.*—(*W. J. Steininger*)

**Fluid Motion in Hydropneumothorax.**—When fluid collects in a pneumothorax space, the fluid level usually moves in the same direction as the diaphragm; it moves downward during inspiration and upward during expiration. However, an inverse movement is often noticeable. In the majority of cases this phenomenon can be explained by the fact that some lung tissue has come to lie between the diaphragm and the fluid. This part of the lung dilates during inspiration and pushes the fluid upward while the diaphragm moves downward. Conversely, the lung tissue contracts during expiration and the fluid level sinks while the diaphragm moves upward. As a rule, the inverse movement therefore indicates interposition of lung tissue between fluid and diaphragm (Authors' Summary).—*Mouvement inversé du niveau liquidien de l'hydro-pneumothorax, signe d'un processus symphysaire de la base pulmonaire, G. Rossel & J. G. Berthet, Schweiz. Ztschr. Tuberk., 1949, 6: 181.*—(*E. Dunner*)

**New Roentgen Kymograph.**—The so-called mechanical factors cannot be excluded from conceptions of the mode of action of collapse therapy on tuberculous pulmonary cavities. One reason for cavities persisting after extensive, technically satisfactory thoracoplasties is that the diseased area is still affected by distention and retraction caused by pulmonary elasticity and respiratory dynamics. The site of the lesion, the effects exerted on it by the motion of the diaphragm, and the mobility of the mediastinum are factors which cannot be ignored. Methods affording added information as to the effect of thoracic motion on cavity walls are therefore of utmost significance. A new roentgen kymographic apparatus consists of a grid having cross slits at right angles to one other. Behind this grid the film rotates clockwise through 90 degrees during each exposure. The center of the grid is placed by fluoroscopy so that it coincides with the center of the cavity. The patient is instructed to breathe slowly, the rotation of the film is started, and the exposures are made. The films obtained

clearly demonstrate by concentric curves the influence of motion within a certain radius of a cavity.—*Kimographe rotatif pour l'étude des cavernes pulmonaires, L. de Carvalho, A. De Sousa, & C. Vidal, Schweiz. Ztschr. Tuberk., 1949, 6: 79.*—(*E. Dunner*)

**Tomography of Tuberculous Spondylitis.**—Earlier roentgenographic diagnosis of tuberculosis of the spine is important. As recently reported by Schinz, 90 per cent of the patients at the University of Zürich Clinic had symptoms for approximately a year before a recognizable roentgenographic change in the vertebrae was detectable. Early diagnosis of tuberculous spondylitis can be obtained and the course of the disease more readily followed by using tomograms of the spinal column.—*Beitrag zur Tomographie der Spondylitis tuberculosa, E. Sommer, Schweiz. Ztschr. Tuberk., 1949, 6: 189.*—(*E. Dunner*)

## Clinical Studies, Nontuberculous Disease

**Epidemic Pulmonary Disease.**—In the past five years an unusual and perhaps new pulmonary disease has been described in three previous articles. This has been called (*1*) "primary atypical penumonia", (*2*) "an unusual pulmonary disease," and (*3*) "cave sickness, a new disease entity (*?*)." The three epidemics of this disease were reported from southeastern Oklahoma, Missouri, and southwestern Arkansas. In one epidemic, all of the patients had been in a storm cellar; in another, all had been in an abandoned chalk mine. The cause of these epidemics has not been found, the bacteriologic and viral studies of sputum, blood, and tissues, as well as various blood agglutinations, having all been noncontributory. Clinically the disease is characterized by severe constitutional symptoms, absence of physical signs, diffuse infiltrations of the parenchyma of the lungs, and prolonged convalescence marked by vague pains in the thorax, low grade fever, malaise, and persistent roentgenographic changes. In many cases, the roentgenographic picture resembled advanced miliary tuberculosis. The incubation period varied from four to eighteen days and the onset was usually sudden. About 65 per cent of the patients had severe chills; others complained of chilly sensations. The pulse rate and respiratory rate did not parallel the temperature. Many of the patients had evidence of hemoconcentration. Headache was a major symptom. The prognosis is excellent as no deaths have occurred. The morbidity, however, was marked and many of the patients were unable to return to work for four to six months. Dyspnea was out of proportion to the clinical and roentgenographic findings during convalescence. Supportive measures only have been used as indicated.—*Epidemic pulmonary disease, J. C. Cain, M. Clin. North America, July, 1949, 33: 1099.*—(*B. Hyde*)

**Histoplasmosis.**—Histoplasmosis has been known in humans since 1906 and in animals, including mice, rats, and dogs, since 1939. Almost 3 per cent of rats in Virginia have revealed positive cultures for the fungus *H. capsulatum*. Reported cases of canine histoplasmosis would seem to indicate that the dog cannot be overlooked as a possible reservoir of this disease although the disease was not transmitted to dogs kept in the same cage with an infected dog. Five dogs with negative histoplasmin skin tests were infected with *H. capsulatum* from a human case by injection directly into the right lung. All but one of the 5 dogs showed progressive lung involvement on roentgenograms. Each lost weight and the general condition became poor. Fever developed three to four days following infection and continued for three to four weeks or until shortly before death. The dogs died one, two, and six weeks after infection. Weekly skin tests with histoplasmin in a 1:100 dilution showed that all dogs, except the one which died two weeks after inoculation, developed skin sensitivity within three weeks. Complement fixation tests could not be used because the blood was anticomplementary. At autopsy *H. capsulatum* was cultured from various organs, including the lung, mediastinal

lymph nodes, spleen, adrenals, glands, and liver.—*A review of histoplasmosis, J. S. Ruhe & P. D. Carver, J. Am. Vet. M. A., July, 1949, 115: 47.*—(L. Hyde)

**Histoplasmosis in Brazil.**—Among 202 patients examined for tuberculosis at a Rio de Janeiro dispensary, 53 (26.2 per cent) reacted to histoplasmin. Forty-seven of these gave a positive tuberculin reaction as well. Eight of the group showed abnormal pulmonary shadows. Pulmonary calcification was present in 13 patients who were positive both to histoplasmin and tuberculin, and in one who was histoplasmin-positive and tuberculin-negative. The group included both white and Negro patients from widely separated parts of Brazil, showing the wide distribution of the disease. Roentgenographic findings in lungs of histoplasmin-positive cases were very similar to those reported from the United States. While the number of cases is inadequate for definite conclusions, age seemed to be a factor as it is in tuberculin allergy. There was a slighter predominance in males. The first case of histoplasmosis in Brazil was diagnosed by Vilela and Pará in 1941 in a Negro child, three years old, from Minas Gerais. Among 169,808 liver specimens examined by these same workers, 5 were found pathologically positive for visceral histoplasmosis. Almeida and Lacaz in 1941 reported 2 cases in children from Sao Paulo, and Duarte reported one case in a Negro woman at Rio de Janeiro. All of these cases were fatal.—*Sôbre a histoplasmose: I. Conceito moderno: Histoplasmose maligna e benigna. Histoplasmose infecção. II. Estudo baseado em 53 indivíduos reatores positivos á histoplasmina na cidade do Rio de Janeiro, A. de Carvalho, Clín. Tisiol., January–March, 1949, 4: 51.*—(*A. A. Moll*)

**Residual Coccidioidomycotic Lung Lesions.**—Coccidioidomycosis can no longer be considered a rare disease confined to the San Joaquin Valley in California. Most of the western states contain endemic areas in which the incidence of infection in military personnel was found to be as high as 55 per cent, totally independent of the length of time spent in such areas. Cases of infection have been reported in people who have only driven through an endemic area. Any individual who presents a persistent pulmonary infiltration in which the diagnosis cannot be readily established should be closely questioned as to possible exposure. The authors present 20 veterans who had residual lesions of pulmonary coccidioidomycosis, persisting from two to five years after the initial infection. The pulmonary lesions were of various types: nodular densities, cavities, mottled infiltrates, fibrosis, pleural effusion, and calcification. Skin sensitivity was found to diminish with lapse of time. Tuberculosis was excluded by negative laboratory studies and positive coccidioidin and complement fixation reactions. Most of the patients were asymptomatic.—*Residual pulmonary lesions in coccidioidomycosis, H. E. Bass, A. Schomer & R. Berke, Arch. Int. Med., December, 1948, 82: 519.*—(*E. A. Rouff*)

**Nocardiosis.**—Infections in man due to the aerobic and sometimes acid-fast *Nocardia asteroides* are rare as compared to those due to the anaerobic *Actinomyces bovis*. In 37 cases of infection with *Nocardia asteroides* collected from the literature, the mortality rate appears high. Only 5 cases could be considered as having recovered, and all 5 patients received sulfonamide therapy in addition to other forms of treatment. The infection was pulmonary in 33 cases, and metastatic abscesses of the brain were present in at least 11. The authors report 3 cases of nocardiosis due to *Nocardia asteroides*, 2 of them terminating fatally. The organisms isolated from the lesions belong to the relatively rare aerobic group of *Actinomyces* whose acid-fastness is variable. In distinguishing *Nocardia asteroides* from other pathogenic *Actinomyces*, emphasis should be placed on the readiness with which they may be cultivated on artificial mediums, their cultural characteristics, their virulence for laboratory animals, and the absence of "sulfur granules" or "club for-

mation" at the periphery of the mycelial masses. The importance of the actinomycotic infections lies in the possibility of their being confused with tuberculosis. Nocardiosis should be considered in all patients with obscure or unusual chronic infections, especially when repeated attempts to demonstrate tubercle bacilli have failed. The treatment of choice in the aerobic type of actinomycotic infection appears to be sulfadiazine or other sulfonamides rather than antibiotics such as penicillin or streptomycin.—*Nocardiosis with a report of three cases of actinomycosis due to Nocardia asteroides, F. C. Tucker & E. F. Hirsch, J. Infect. Dis., July–August 1949, 85: 75.—(F. G. Petrik)*

**Influenza Virus in Pneumonia.**—Because there has been increasing evidence that the influenza virus plays a role in the etiology of pneumonia, sputum and sera of pneumonia patients were examined during influenzal epidemic and interepidemic periods. Of 36 cases of pneumococcal pneumonia occurring in Baltimore during an epidemic of influenza A, 17 yielded positive evidence either by virus isolation or by seriological studies of recent or concurrent infection with influenza virus. The strains of virus were similar to those isolated from uncomplicated cases in the epidemic. In the interepidemic period the virus was isolated from one sputum only in a series of 33 cases of pneumonia studied. It was, however, found in 2 cases of fatal primary pneumonia and in 2 cases of fatal secondary pneumonia in this period. In no case was the virus isolated from nasal washings of 100 cases of uncomplicated upper respiratory infection studied in this same interepidemic period. The generally accepted explanation concerning the relationship of influenza virus and bacteria in pneumonia accompanying influenza is that the virus plays only a preparatory role. These studies are believed to indicate that influenza virus plays a role in the etiology of certain pneumonias which have hitherto been considered primarily bacterial in origin.—*The relationship of influenza virus and bacteria in the etiology of pneumonia.—E. Maxwell, T. Ward, & T. Van Metre, Jr., J. Clin. Investigation., March 1949, 28: 307.—(S. Hadley)*

**Idiopathic Hemosiderosis.**—Acute idiopathic pulmonary hemosiderosis is a rare, nonoccupational disease. The case presented is that of a two and-one-half-year-old girl with increasing pallor, lassitude, and general debility. On admission the child was uninterested in her surroundings. Her pulse was rapid but regular; there were no abnormal signs in the chest. A severe hypochromic anemia with leukopenia was present and transfusion with one pint of packed cells produced dramatic improvement. A chest roentgenogram revealed diffuse reticulation throughout the lung fields, more pronounced near the hilar regions. A tuberculin test was negative. A further transfusion with packed cells effected improvement but another roentgenogram showed increase in the mottling of the lung fields. Despite the use of oxygen, penicillin, and cardiorespiratory stimulants, the child died. In the roentgenograms the reticulation of the lung fields consisted of small aggregations about the size of those in miliary tuberculosis, sarcoidosis, or following lipiodol instillation. The densities of reticulation were maximal near the hilar regions and diminished toward the periphery. There was no gross nodulation such as is common in the pneumoconiosis group. At autopsy there were mutliple subpleural petechial hemorrhages, a small effusion, and recent pleural roughness. The pleura was deep purple, whereas the lung parenchyma was brown and similar to that in ordinary brown induration. The lung was solid, airless, and heavy. The alveoli were crammed with phagocytic cells containing free iron and there was considerable recent intra-alveolar hemorrhage. No obvious deficiency of the elastic tissue was noted. No free iron was present in the spleen liver, or lymph nodes, nor elsewhere in the reticulo-endothelial system. There was no evidence of tuberculosis, sarcoidosis, or silica deposits. It has been postulated that this disease is caused by an unidentified hemolytic

agent but investigation fails to detect hemolysins. Another postulate is that this condition may be caused by a general breakdown of the alveolar framework although this was not confirmed in the present case in which the eleatic tissue appeared normal. This condition is also described associated with mitral stenosis but no evidence of cardiac disease was found in this child.—*Acute idiopathic pulmonary haemosiderosis, L. Nancekieville, Brit. M. J., March 12, 1949, No. 4601: 431.*—(*R. W. Clarke*)

**Hemosiderosis in Mitral Disease.**—Nodular lung densities simulating pneumoconiosis or miliary tuberculosis may occur in mitral disease. In such instances the lesions are due to a deposition of hemosiderin in the lungs. Similar lesions have been reported in lungs of arc welders, silver finishers, and grinders of ferrous metals. In these three occupations the siderosis is, of course, exogenous in origin. Endogenous siderosis of the lungs may occur in children with severe anemia or in patients with mitral heart disease. The authors report 6 cases of the latter group; 4 were verified at autopsy. The nodules were visible to the naked eye, they stained with Prussian blue, and varied in size from 1 to 3 mm.—*Hemosiderosis of the lung due to mitral disease, E. P. Pendergrass, E. L. Lame & H. W. Ostrum, Am. J. Roentgenol., April, 1949, 61: 443.*—(*J. E. Farber*)

**Disseminated Ossification of the Lungs.**—Disseminated ossification may be either (*1*) trabecular in the senile lung, or (*2*) nodular and circumscribed in the lungs of younger people with mitral disease. The latter was observed in a 39-year-old woman with long-standing, progressive dyspnea and ankle edema. A month previous to admission she had a cough productive of grayish sputum. She had had rheumatic fever at the age of twenty and presented the signs and symptoms of mitral disease. There were signs of consolidation at the right base with a pleural rub in the right axilla. She received sulphamezathine and penicillin, but remained febrile. Her sputum became blood-stained and her liver enlarged. Chest roentgenograms showed midzone shadows of the congestive type, the lung fields displaying generalized miliary shadowing, more intense in the basal zones. The nodules were discrete and 0.5 to 2.0 mm. in diameter. The heart was enlarged. In a later film an effusion was seen on the right; the opacities remained unchanged. She died suddenly, and at autopsy there was a typical mitral stenosis. The lungs showed numerous large and small infarcts, some of which were suppurative. The pleurae were studded with miliary calcified plaques. Throughout the lung substance there were numerous microscopic, rounded, bony nodules with irregularly crenated outlines. Vessels were present in the bone but no medullary cavities were seen. A striking feature was that most of these nodules were not surrounded by fibrous tissue. The etiology of this condition is obscure although it is always associated with advanced rheumatic mitral stenosis. It is suggested that the bone may arise from organization of congestive hemorrhages or of intra-alveolar collections of pigment-bearing phagocytes.—*Disseminated ossification of the lungs in association with mitral stenosis, H. M. Lawson, Brit. M. J., March 12, 1949, No. 4601: 433.*—(*R. W. Clarke*)

**Chronic Nonspecific Pneumonitis.**—Ten patients, aged 30 to 61 years, had a gradual onset of productive cough, hemoptysis, and chest pain. Bronchograms showed blunting of the bronchi rather than dilation. Bronchoscopy showed inflammation and pus formation in the involved bronchi in 8 of the 10 cases. With postural drainage and sulfa drugs some showed transient improvement but the disease ultimately was progressive. Surgical drainage or resection was used in 9 cases with complete recovery in all but one patient, who died five days after operation. Five patients had lobectomy and 2, with a preoperative diagnosis of carcinoma, had pneumonectomy. The removed tissue showed interlobular fibrosis and thickening of the alveolar walls. The microscopic diagnosis was chronic diffuse

pneumonitis. The authors feel that these cases represent a disease meriting separate classification.—*Chronic nonspecific suppurative pneumonitis, R. Kershner & W. Adams, J. Thoracic Surg., August, 1948, 17: 495.—(R. E. MacQuigg)*

**Lung Lesions in Rheumatoid Arthritis.**—A boy, aged six, was admitted with swelling of the right knee and ankle and a palpable liver. Juvenile rheumatoid arthritis was diagnosed and he was given two courses of gold therapy, despite which the disease progressed. After a mild tonsillitis, he experienced a slight increase in malaise with intermittent fever. Over eight days his temperature increased to 101.8 and then subsided by lysis. A Mantoux test was negative. The chest roentgenogram showed diffuse shadows radiating from the hilum; these were present for about two months. Pulmonary congestion from left heart failure, possibly precipated by a blood transfusion given three weeks before, was a possible explanation of the pulmonary episode, but there was no evidence of heart disease and recovery was rapid without treatment.—*Pulmonary lesions in rheumatoid arthritis, D. G. Leys & P. N. Swift, Brit. M. J., March 12, 1949, No. 4601: 434.—(R. W. Clarke)*

**Pulmonary Collapse in Pertussis.**—In 44 children with pertussis severe enough to warrant hospitalization, there was clinical and roentgenological evidence of lobar or segmental collapse, usually of the middle or lower lobes. Collapse of over two months' duration was seen in one of 4 mild cases, 9 of 16 moderate cases, and 13 of 17 severe cases. Postural drainage and heavy percussion over the affected lobe were used to induce cough and relief of bronchial obstruction. Patients who do not show evidence of re-expansion on this regimen should be bronchoscoped and watched closely for the development of bronchiectasis.—*Pulmonary collapse in pertussis, D. P. Nicholson, Arch. Dis. Childhood, March, 1949, 24: 29.—(E. A. Rouff)*

**Pancreatic Cystic Fibrosis.**—In an unusual case of cystic fibrosis of the pancreas the patient lived until the age of 17 years. The boy was underdeveloped and had had steatorrhea since shortly after birth. Chronic cough and shortness of breath had been present since the age of ten years when he had measles complicated by pneumonia; clubbing of the fingers and toes was present. The patient died of bronchopneumonia. The outstanding findings at autopsy were chronic pulmonary suppuration with squamous metaplasia of the bronchial epithelium, cirrhosis of the liver, and almost complete replacement of acinar elements of the pancreas by fat and fibrous tissue. Cystic fibrosis of the pancreas usually is accompanied by chronic pulmonary suppurative disease. It has been suggested that vitamin A deficiency results in squamous metaplasia of the bronchial epithelium; the consequent loss of cilia leads to impaired drainage of bronchial secretions. It also has been stated that secretions are unusually viscid in cystic fibrosis and that tenacious bronchial secretions contribute to partial obstruction and infection.—*A case of cystic fibrosis of the pancreas associated with chronic pulmonary disease and cirrhosis of the liver, H. E. Pugsley & P. McK. Spence, Ann. Int. Med., June 1949, 30: 1262.—(H. R. Nayer)*

**Electrophrenic Respiration.**—Electrical stimulation of the right phrenic nerve was carried out on a patient in whom the left phrenic nerve had been crushed for the relief of severe chronic diaphragmatic flutter. Observations indicated that (*1*) a gradual smooth diaphragmatic contraction occurs when increasing voltage is applied to the phrenic nerve; (*2*) respiratory minute volumes in excess of the patient's spontaneous minute volumes can be obtained with submaximal stimulation; (*3*) adequate oxygenation of the blood can be maintained even in the absence of spontaneous respiration, the depth being proportional to the peak voltage applied; (*4*) the human subject completely relinquishes spontaneous control of respiration when electrophrenic respiration is induced. It is of in-

terest that, although the procedure is not a painful one, the patient experienced discomfort referred to the shoulder along the ridge of the trapezius muscle.—*Electrophrenic respiration. II. Its use in man, J. Whittenberger, S. Sarnoff, & E. Hardenbergh, J. Clin. Investigation, January, 1949, 28: 124.*—(*S. Hadley*)

**Enzyme Treatment of Empyema.**—Intrapleural injections were made of concentrated and partially purified preparations derived from cultures of hemolytic streptococci. The active components of these preparations are: (*1*) a fibrin-lysing substance, streptokinase, which may act as a catalyst causing the transformation of a zymogen of normal human blood, plasminogen, into a proteolytic enzyme, plasmin, which dissolves fibrin; and (*2*) desoxyribonuclease which depolymerizes the desoxyribonucleoproteins. The latter substances make up 30 to 70 per cent of pus and are responsible, at least in part, for the fibrous, gelatinous nature of purulent material. In a group of patients with acute fibrinous pleurisy all showed a rapid drop of fibrinogen in the pleural fluid with treatment. This lasted for ten days to one month. In a group with bacterial empyemas in which fibrinogen is normally absent, rapid and extensive liquefaction of nucleoproteins of the empyema facilitated drainage remarkably. In 2 patients with hemothorax, streptokinase injected into the thorax allowed a striking drainage of a previously extensively loculated hemothorax by liquefaction of the fibrin. Applications of this therapy in conjunction with surgery may be used to advantage. Toxic manifestations consist of mild pyogenic response with general malaise and local outpouring of leukocytes of a few days' duration.—*The effect in patients of streptococcal fibrinolysin (Streptokinase) and streptococcal desoxyribonuclease on fibrinous, purulent, and sanginous pleural exudates, W. Tillett & S. Sherry, J. Clin. Investigation, January 1949, 28: 173.*—(*S. Hadley*)

**Medical Treatment of Pulmonary Abscesses.**—The general practitioner and internist are responsible for the death of one-third of the patients who have developed pulmonary abscesses. A review of 2,166 cases was undertaken in the hope of improving medical treatment. Bed rest is imperative in suppurative pulmonary disease and, once an abscess has developed, drainage is essential. Medical drainage is accomplished by posture and is frequently improved by periodic bronchoscopic aspirations. Bronchoscopy should be done at least once in every patient over 30 years of age to help exclude neoplasm. Medical treatment of chronic abscess is ineffective although transient improvement may be obtained with antibiotics. The internist often contributes to failures because he fails to identify the etiological agent, gives inadequate treatment, and, when the patient has made partial recovery, prolongs the medical treatment until the patient is a poor surgical risk. The mortality is 32.7 per cent for the patients treated surgically and 34.7 per cent for those treated medically. Part of the high surgical mortality results from poor medical treatment prior to operation. Sulfonamide therapy is definitely helpful in abscesses caused by gram-positive cocci. In fusospirochetal infections it gives temporary benefit only. If the patient is not clearing steadily on serial roentgenograms by the end of the fourth to sixth week, he should be referred to the thoracic surgeon.—*Medical treatment of acute and chronic pulmonary abscesses, D. T. Smith, J. Thoracic Surg., February, 1948, 17: 72.*—(*R. E. MacQuigg*)

**Micronized Aminophylline for Asthma.**—Inhalation of particulate xanthine aerosols when they are used in an inhalator similar to that for micronized penicillin has proved to be an effective form of symptomatic therapy in 30 of 35 cases of chronic bronchial asthma. The relief is rapid and satisfactory in most mild and moderate cases. In severe attacks the duration of relief is usually short (20 to 40 minutes), but repeated doses have maintained satisfactory control in numerous instances and have prolonged the interval between such injections as are required. This method of administration is particularly useful in the symptomatic treatment of

ambulatory cases of chronic asthma and is free of important side reactions. Overdosage is seldom encountered because the effective dose by inhalation (60 mg.) is relatively small. The clinical response and symptomatic relief obtained from inhaled micropowdered xanthines were evaluated primarily on the basis of objective measurements with a recording spirometer. The vital capacity increased 21 per cent on the average. The important psychogenic factors were reduced to a minimum by the control measures and placebos employed during the investigations. —*Micropowdered aminophylline or theophylline inhalation therapy in chronic bronchial asthma. Evaluation by recorded vital capacity changes, G. V. Taplin, A. L. Gropper, G. Scott & J. R. Hageman, Ann. Allergy, July–August, 1949, 7: 513.*—(*L. Hyde*)

**Sympathectomy for Asthma.**—Structures innervated by the sympathetic system become more sensitive to epinephrine after denervation, and sensitization of the patient to his own epinephrine may explain the beneficial effect of sympathetic denervation. The nerve supply to the lungs is derived from vagus and sympathetic trunks through fibers forming the posterior pulmonary plexus behind the hilum. Levin injected with alcohol the dorsal sympathetic ganglia in 23 asthmatic patients; 75 per cent obtained complete relief and there was some improvement in the remainder. Excision of the posterior pulmonary plexus is the most certain method of eliminating all extrinsic nerve stimuli to the lung. Reinhoff and Gay reported excellent results in 27 asthmatic patients following excision of the plexus. In poor risk cases, however, less drastic surgery would be preferable, prompting the authors to resect bilaterally the thoracic ganglia, 2 through 5, in 5 asthmatic patients. All were improved, including those now followed for ten years.—*Dorsal sympathetic ganglionectomy for intractable asthma, D. Carr & H. Chandler, J. Thoracic Surg., February, 1948, 17: 1.*—(*R. E. MacQuigg*)

**Esophageal Hernias of the Short Esophagus Type.**—From 1935 through 1945, 220 cases of esophageal hernias of the short esophagus type were seen comprising 10 per cent of thiaal hernias. Symptoms were diverse and of varying severity; 75 per cent noted dysphagia. Esophagoscopy may be necessary to determine the type of hiatal hernia. The short esophagus has been assumed to be congenital. Evidence now indicates that shortening follows peptic ulceration of the esophagus with healing and contraction. Recent studies also showed that direct or indirect stimulation of the vagus nerve in dogs results in reflex shortening of the esophagus. Of the cases discussed 78 per cent are felt to have been acquired and only 4 per cent congenital. Patients with this lesion are not good candidates for surgical repair. Of 4 patients who had left phrenic interruption, 3 were benefited. Another 17 had an abdominal operation but dysphagia was best treated by dilatation over a previously swallowed thread. Bland diet, antacid preparations, elevation of the head of the bed 12 to 15 inches, and weight reduction are recommended as effective.—*Esophageal hiatal hernias of the short esophagus type: Etiology and therapeutic considerations, A. Olsen & S. Harrington, J. Thoracic Surg., April, 1948, 17: 189,* (*R. E. MacQuigg*)

**Traumatic Diaphragmatic Hernia.**—Two cases of strangulation of the stomach and traumatic diaphragmatic hernia were treated successfully by transthoracic reduction. Of the 4 similar cases in the literature, 3 were fatal. It is recommended, therefore, that a traumatic diaphragmatic hernia be repaired transthoracically as soon as it is diagnosed and before obstruction can occur.—*Strangulation of the stomach and traumatic diaphragmatic hernia, D. J. Dugan & P. S. Samson, J. Thoracic Surg., December, 1948, 17: 771.*—(*R. E. MacQuigg*)

**Esophageal Diverticula.**—The pulsion type of esophageal diverticulum may fill with food and obstruct the esophagus by mechanical angulation. In 3 patients with this disorder

diverticulopexy was done. Two other patients seen after the advent of penicillin were treated by one-stage excision through the left posteriolateral approach. This is felt to be the procedure of choice. All 5 patients obtained complete relief of dysphagia and anorexia.—*Diverticula of the thoracic esophagus, H. Adams, J. Thoracic Surg., October, 1948, 17: 639.—(R. E. MacQuigg)*

**Pulmonary Cysts.**—Overdistended emphysematous bullae may give rise to symptoms. These result from either stenosis of a small bronchus with resulting alveolar overdistention or ulceration of the wall of such a bronchus with escape of air into the interstitial tissues. There is usually a previous history of acute or chronic respiratory disease. Much of the lung may be replaced by cysts, and severe dyspnea and even death by asphyxia may result. The cysts also may cause symptoms by: (*1*) becoming infected, (*2*) causing pain and (*3*) giving reflex dyspnea by the tension within them. It is possible that an isolated area of lung which has become overinflated can influence the Hering-Breuer reflex to the extent that the depth of respiration becomes limited and thus causes dyspnea. On the basis of this theory, phrenic crush was performed on a patient who had dyspnea out of proportion to the size of a very small cyst of the right lower lobe. This procedure gave relief; when diaphragmatic motion returned, the symptoms reappeared. In the case of a very large cyst, the greater part of its wall was excised and the bronchus was stitched. If the cyst is located in or adjacent to a bronchiectatic lobe, lobectomy is indicated. The cysts never should be needled because of danger of producing a tension pneumothorax.—*Giant bullous cysts of the lung, P. R. Allison, Thorax, December, 1947, 2: 169.—(A. G. Cohen)*

**Lesions Simulating Bronchiogenic Carcinoma.**—When carcinoma arises in a bronchus which cannot be seen bronchoscopically, early diagnosis may be difficult. In 300 cases of proved bronchiogenic carcinoma, positive bronchoscopic diagnosis could be made in only 45 per cent of the patients, the remaining being diagnosed clinically. The lesion was resectable in only one-sixth of the cases. Exploration should be carried out whenever peripheral lung cancer is a strong possibility, and the removal of a nonmalignant pulmonary lesion is not always a "surgical error" since most of the patients are cured by the excision. In a series of 30 cases of benign lesions removed because carcinoma was suspected, there were 20 inflammatory lesions, including 6 lung abscesses and 5 tuberculomas. There were 6 benign tumors, including 3 adenomas and 4 developmental anomalies, of which 3 were cysts and one was thyroid tissue. Of the 30 patients, 27 were cured by the operation, 2 were improved, and one died postoperatively. In cases of lung abscess, the cavity may be secondary to bronchial obstruction from malignancy, and resection is the procedure of choice for an abscess that does not respond promptly to conservative measures. In an expanding peripheral lesion it is often unwise to wait the six weeks for bacteriological studies and there is evidence that it is wise to resect so-called "tuberculomas" while the sputum is still negative. Most bronchial adenomas of the bronchus come to surgery eventually because of infection or hemorrhage and are all potentially malignant so that early excision is the treatment of choice. Frozen sections aid in deciding at operation between pneumonectomy and lobectomy. The management of a suspected bronchiogenic carcinoma has now reached a status like that of suspected carcinoma of the breast.—*Nonmalignant intrathoracic lesions simulating bronchiogenic carcinoma, L. Brewer, W. Jones & F. Dolley, J. Thoracic Surg., August, 1948, 17: 439.—(R. E. MacQuigg)*

**Intrathoracic Goiter.**—In true intrathoracic goiter, the largest diameter of the tumor lies in the mediastinum below the thoracic inlet. Most of them lie anteriorly; a few lie posteriorly. Six cases of the latter are reported. There

is always a pedicle-like connection, which often is small, with the thyroid in the neck. The tumor lies in the farthest posterior aspect of the mediastinum against the vetebral column and tends to press the esophagus to the right or left. It rarely disturbs the relationships of the trachea except to displace it forward slightly. When it is very large, the tumor may encroach upon the upper lobe of one of the lungs. It lies behind the recurrent laryngeal nerve and inferior thyroid artery and arises from the posterior and lateral aspect of the lateral lobe of the thyroid rather than from the inferior aspect. The posterior tumor may be more difficult to remove through the neck as the aperture is small, so that an intrathoracic approach may be needed. Of 6 cases, this was mandatory in 2 and preferred in one. Five patients had cough, which was troublesome in 2. Dysphagia occurred in 2 and moderate dysphonia in one. The presence of the tumor alone is indication for operation.—*Intrathoracic goiter located in the posterior mediastinum, R. H. Sweet, Surg., Gynec. & Obst., July, 1949, 89: 57.—(A. G. Cohen)*

**Solitary Chest Tumors.**—There are no roentgenographic findings that can be considered characteristic of any particular type of solitary tumor within the chest. Needle biopsy carried out under biplanar roentgenoscopic guidance was performed in 31 of 50 cases of such tumors with positive results in 23 instances. No deleterious effects were noted. In 2 cases aneurysm of the innominate artery was diagnosed without difficulty by aspiration through a small gauge needle.—*Solitary tumors of the chest, Am. J. Roentgenol., July, 1949, 62: 52.—(T. H. Noehren)*

**Pulmonary Xanthoma.**—A 34-year-old woman with hemoptysis was found to have a tumor in the right lower lobe. Lobectomy demonstrated that it was a solitary xanthoma. No other abnormalities could be found. She has remained well during the succeeding nine months. This is the first reported case.—*Solitary xanthoma of the lung, H. W. Scott, Jr., A. G. Morrow, & T. P. B. Payne, J. Thoracic Surg., December, 1948, 17: 821.—(R. E. MacQuigg)*

**Primary Rib Tumors.**—There are recorded 111 proved cases of primary rib tumor and the authors add 7. Symptoms are pain, which may occur alone, and tumor. Since metastases are more common than primary growths and may be noted before symptoms are produced by the primary tumor, thorough study of each case is indicated. Exploratory biopsy is far better than watchful waiting. Irradiation therapy is useless; early, wide excision should be done to include the underlying pleura well beyond the lesion along with any adjacent muscles. Complete removal of the first rib has been advocated for malignancy involving any portion of it since in this vascular area partial resection is frequently followed by metastases.—*Primary rib tumors, R. Dorner & D. March, J. Thoracic Surg., October, 1948, 17: 690.—(R. E. MacQuigg)*

**Pneumothorax with Metastatic Sarcoma.**—The association of spontaneous pneumothorax with metastatic tumors in the lung is rare. Only 2 cases have been reported previously. The authors describe 3 other cases of spontaneous pneumothorax associated with metastatic sarcoma. All the patients were young males: one had a fibrosarcoma primary in the neck, another an osteogenic sarcoma primary in the tibia, and the third an angiosarcoma primary in the retroperitoneal space. In all cases the extensive pulmonary metastases were recognized early and in each instance pneumothorax was known to exist for weeks prior to death. Peripheral tumor nodules sometimes produce partial bronchiolar obstruction. Through a ball-valve action alveolar walls may rupture, with the consequent escape of air into the interstitial spaces and pleural cavity. Only occasionally are these nodules so strategically located as to cause significant interstitial emphysema and pneumothorax.—*Spontaneous pneumothorax associated with metastatic sarcoma: A report of*

*three cases, E. A. Lodmell & S. C. Capps, Radiology, January, 1949, 52: 88.—(W. J. Steininger)*

**Origin of Sputum in Lung Cancer.**—From an examination of all the lungs or lobes removed for neoplasm at the Mayo Clinic during twelve years, it was concluded that the sputum could be correlated with the "obstructive pneumonitis" distal to the tumor. The authors feel that this lesion should be distinguished from other forms of "atelectasis." The obstructed portion at first appears as a "drowned lung" and then becomes fibrotic with physiologic obliteration of the arteries and veins. Less commonly, abscesses form. The mucopurulent fluid accompanying pneumonitis forms most of the sputum in the majority of patients who have neoplasms of the bronchus but complete obstruction is not necessary to prevent the egress of secretions. In some cases evacuation of necrotic centers of tumor masses produces a sudden onset of voluminous sputum.—*Obstructive pneumonitis of neoplastic origin, J. R. McDonald, S. W. Harrington & O. T. Clagett, J. Thoracic Surg., February, 1949, 18: 97.—(R. E. MacQuigg)*

**Bronchial Smears in Cancer.**—Sputum for examination was fixed immediately in 70 per cent alcohol. Smears of bronchial washings were fixed in alcohol-ether, stained in hematoxylin, and then in OG6 and EA65. In 1,200 cases there were 4 false positive reports from cases of bronchiectasis which can now be correctly identified by characteristic features of the cells. In no case reported as Class V (definitely positive) has the diagnosis been disproved. Of 74 cases operated upon, 7 had a Class V report on the sputum or bronchial washing as the only positive preoperative histologic evidence. In 236 cases proved eventually to be bronchiogenic carcinoma, there were 112 positive sputum reports and 29 positive bronchial washings, a positive cytologic diagnosis in 60 per cent. In the 176 cases bronchoscoped there were 37 per cent positive biopsies.—*Cytology of bronchial secretions, W. L. Watson, H. Cromwell, L. Craver & G. N. Papanicolaou, J. Thoracic Surg., February, 1949, 18: 113.—(R. E. MacQuigg)*

**Pulmonary Arteriovenous Fistula.**—A review of 22 published cases of pulmonary arteriovenous fistula shows the symptoms and signs, in order of frequency, to be: (*1*) roentgenographic evidence of pulmonary abnormality, (*2*) cyanosis, (*3*) polycythemia, (*4*) clubbing of fingers, (*5*) murmurs over the affected lung, (*6*) hemoptysis. Whenever any combination of these signs is encountered clinically, an arteriovenous fistula of the lung should be suspected, and angiography should be performed. It is important to employ a device for the rapid changing of films in order not to miss the salient features. The case is presented of a 26-year-old male who had four severe hemoptyses within eighteen days. He was found by angiography to have an arteriovenous fistula of the right lower lobe and was cured by lobectomy.—*The angiographic demonstration of pulmonary arteriovenous fistula, C. E. Duisenberg & L. Arismendi, Radiology, July, 1949, 53: 66.—(W. J. Steininger)*

**Surgery for Bronchopulmonary Moniliasis.**—The first case of bronchopulmonary moniliasis successfully treated by surgical excision is reported. Vaccine and drug therapy have been sporadically successful. The diagnosis is difficult, as skin tests are equivocal and *Monilia* in the sputum may be nonpathogenic or secondary invaders. The sputum in this case was scanty and not characteristic.—*A report of a case of localized bronchopulmonary moniliasis successfully treated by surgery.—A. Hurwitz & R. Yesner, J. Thoracic Surg., December, 1948, 17: 826.—(R. E. MacQuigg)*

**Resection for Chronic Lung Abscess.**—From 1944 to 1947, 86 cases of lung abscess were treated surgically. In 27 instances drainage was done with rib resection, almost always in one stage; satisfactory results were obtained in 14. Pulmonary resections were done for active abscesses in 52 patients with good

results in 43 (82.7 per cent). There were 2 postoperative deaths. Resections for residuals of abscesses gave satisfactory result in all of 8 cases. Segmented resection is dangerous because of the zone of pneumonitis usually associated with an abscess. Postoperative empyemas occurred in 28.8 per cent of the resections in this series.—*Pulmonary resection for chronic abscess of the lung, R. Shaw & D. Paulson, J. Thoracic Surg., August, 1948, 17: 514.*—(*R. E. MacQuigg*)

**Decortication of Hemopneumothorax.**—Of 43 reported cases of idiopathic spontaneous hemopneumothorax, 33 per cent were fatal. The etiology may be a rupture of an emphysematous bleb or a tearing of pleural adhesions. Blood in the pleural cavity is defibrinated by the motion of the heart, lungs, and diaphragm. The residual plasma will not clot unless fibrinogen is added but frequently, after a few days, a pleural exudate creates a "secondary clot." If blood is not immediately aspirated from the pleural cavity, a thin layer of fibrin is deposited on its walls followed by fibroblastic and angioblastic proliferation in seven days and the formation of fibrous tissue in four weeks. The preferred treatment is early and vigorous aspiration since there is no recurrence of bleeding. If the lung is not completely expanded in three to five weeks, thoracotomy and decortication should be done. A case is described in which no cause for hemothorax was found but which was cured by operation, the first reported, with increase in vital capacity from 1,900 to 4,000 cc. —*Spontaneous hemopneumothorax treated by decortication, P. Elrod & J. Murphy, J. Thoracic Surg., June, 1948, 17: 401.*—(*R. E. MacQuigg*)

**Exploratory Thoracotomy in Empyema.**—Thoracotomy is recommended in any case of empyema which does not respond promptly to chemotherapy, aspiration, closed drainage, and general supportive measures. It may be found that decortication will suffice or that resection is indicated either at the same or at a later operation. An intercostal tube may be placed in an empyema cavity and connected to a water cell resting on the floor, but this procedure is only preliminary to definitive treatment after the red cell volume has been restored and adequate studies, for example, bronchoscopy and bronchography, have been made. The empyema may be secondary to bronchiectasis, subdiaphragmatic abscess, or other condition which can only be corrected by thoracotomy. Otherwise the patient is condemned to an indefinite dependence on drainage tubes or to a chronic sinus and progressive loss of respiratory function. In the author's cases of thoracotomy there were no deaths, and complete rehabilitation was accomplished in a short time.—*Exploratory thoracotomy in the management of pleural empyema, P. W. Sanger, J. Thoracic Surg., December, 1948, 17: 756.*—(*R. E. MacQuigg*)

**Potts Operation for Pulmonary Stenosis.**—One-half of the children with cyanosis because of cardiac abnormality are suitable for operation, the most suitable age being three to seven years. At the time of this report, 26 patients with stenosis (tetralogy of Fallot) and 3 with tricuspid atresia had been operated upon, with 4 deaths, in 3 of which there was brain damage. Results in those surviving surgery have been extremely gratifying.—*Aortic-pulmonary anastomosis for pulmonary stenosis, W. Potts, J. Thoracic Surg., April, 1948, 17: 223.*—(*R. E. MacQuigg*)

**Endobronchial Occlusion for Pulmonary Resection.**—There were postoperative spreads of infection in 21.6 per cent of the pulmonary resections from 1937 to 1947 at Duke University. Methods for controlling these spreads were considered and an endobronchial balloon was devised. It is placed bronchoscopically in the bronchus to be blocked and held there by an inflatable cuff with spurs which engage the bronchial wall. The instrument is not applicable to upper lobectomies. Results in the first 44 cases of resection for suppurative pulmonary diseases are encouraging.—*Endobronchial occlusion during pulmonary resection, J. D. Moody, J. Thoracic Surg., February,* 1949, *18:* 82.—(*R. E. MacQuigg*)

**Anoxia During Surgery.**—Anoxic anoxia with an arterial oxygen unsaturation of 16 to 25 per cent maintained for an hour is said to be harmful to the average healthy individual and very occasionally will be fatal. Measurements of arterial unsaturation were made continuously by means of a Millikan oximeter during and after 70 major thoracic operations. There was no reduction in oxygenation during 15 thoracoplasties but there were surprising swings during thoracotomy. There was an abrupt fall to 25 to 30 per cent unsaturation when the bronchi were sucked out. The return to normal was more rapid if anesthesia with positive pressure up to 15 mm. of mercury was employed. Eleven of 20 cases of thoracotomy showed 8 to 18 per cent unsaturation, increasing gradually during the operation. This also could be prevented by the positive pressure anesthesia. Since anoxia during operation cannot be readily recognized by clinical signs, the use of the oximeter is a valuable addition to the technique of major intrathoracic operations.—*Anoxia during intrathoracic operations, F. Kergin, D. Bean & W. Paul, J. Thoracic Surg., October, 1948, 17: 709.*—*(R. E. MacQuigg)*

**Pathology of Bronchiectasis.**—Seven lobectomy or pneumonectomy specimens were subjected to detailed pathological study of the changes in the various segments. These data were correlated with the preoperative data obtained by bronchography regarding the presence or absence of "involvement." It was found that many of the so-called uninvolved segments were actually the seat of changes. Destructive lesions of the bronchi were uncommon. There were, however, definite inflammatory lesions similar to those found in the affected segments. It could not be determined whether these were progressive nor what the probable course would have been had only segmental resection been done. Sometimes even more advanced lesions were present although bronchograms of the segment had been normal. It is concluded that, in the presence of bronchiectasis in a segment, there are usually changes in adjacent segments not necessarily demonstrable radiographically. The natural history of such lesions following segmental resection is not known and the implications for the type of surgery are obvious.—*Bronchiectasis, a study of the segmental distribution of the pathological lesions, J. R. Moore, S. D. Kobernick & F. W. Wigglesworth, Surg., Gynec. & Obst., August, 1949, 89: 145.*—*(A. G. Cohen)*

**Osseous Lesions of Sarcoidosis.**—The bone lesions of sarcoidosis usually are manifested roentgenologically as a diffuse, coarse, reticular type of bone destruction in the phalanges. The resulting alveolate or lace-like appearance is more common and more characteristic than the widely publicized, circumscribed, "punched-out" foci in the ends of the bones. These rounded defects may be simulated by numerous other conditions whereas the diffuse lesions are virtually pathognomonic. The diffuse forms may progress to produce mutilating deformities, may regress spontaneously, or may resolve into the localized lesions which tend to be more chronic. Transitional forms may be present in the same bone. Of 65 patients with generalized sarcoidosis studies in this series, only 11 (approximately 16 per cent) had definite bone lesions. Despite this low incidence, the unquestioned diagnostic value of demonstrable osseous involvement in a disease notoriously difficult to identify makes it highly desirable to examine routinely the hands and feet of all sarcoidosis suspects throughout the chronic course of the disease.—*The osseous lesions of sarcoidosis, J. F. Holt & W. I. Owens, Radiology, July, 1949, 53: 11.*—*(W. J. Steininger)*

**Electrokymography.**—The electrokymograph is a valuable addition to the methods of study of normal and abnormal cardiovascular pulsations in the chest. In clarity, freedom from artefacts, and ease of correlation with events in the cardiac cycle, it is far superior to the roentgenkymogram. However, the roentgenkymogram provides on a single film considerable information relative to amplitude of pulsations. Use of both

methods in a group of clinical cases has shown that they may be regarded as supplementary, the electrokymogram filling in the finer details which are lacking in the roentgenkymogram. (Authors' Summary)—*Electrokymography of the heart and great vessels, H. M. Stauffer & J. Jorgens, Radiology, April, 1949, 52: 488.—(W. J. Steininger)*

**Angiocardiography.**—Study of over 1,000 patients during eleven years has shown angiocardiography to be a safe and valuable clinical tool. In congenital heart disease, angiocardiography combined with cardiac catheterization makes it possible to diagnose accurately the majority of lesions. Although the anatomical changes are more clearly delineated, contrast visualization adds little information in hypertensive, arteriosclerotic, and rheumatic heart disease. It is of great value in differentiating between pericardial effusion and marked cardiac enlargement. Angiocardiography may be of considerable value in the diagnosis of early syphilitic aortitis. The changes in dissecting aneurysm are distinctive, the aortic lumen being abruptly narrowed and the walls thickened at the site of dissection. In constrictive pericarditis, angiocardiography has revealed the common occurrence of a grossly dilated superior vena cava with a dilated right atrium. The method is helpful in differentiating mediastinal tumors from vascular aneurysms. Benign tumors in the chest usually displace contiguous vessels; malignant tumors tend to produce stenotic and obstructive changes. There is relative pulmonary hypovascularity in tuberculosis; in long standing tuberculosis, fibrosis produces distortion and displacement of the pulmonary vessels. Bronchiectasis is associated with poor filling of the pulmonary arteries supplying the involved areas. In pulmonary emphysema there may be seen striking separation of the pulmonary artery radicles; in atalectasis there is poor filling and crowding together of the vessels. Diminished vascularity is present in pneumothorax. Following pneumonectomy, increased circulation to the remaining lung is often shown by the presence of an enlarged branch of the pulmonary artery.—*Clinical angiocardiography, C. T. Dotter & I. Steinberg, Ann. Int. Med., June 1949, 30: 1104.—(H. R. Nayer)*

## Antimicrobial Therapy

**Dihydrostreptomycin for Pulmonary Tuberculosis.**—Twenty patients with pulmonary tuberculosis were treated with dihydrostreptomycin and were studied carefully for toxic effects. Ten patients each received daily 2 or 3 Gm. of the drug for a period of 90 days. Eosinophilia was less conspicuous than with streptomycin. One patient developed transitory renal irritation; this compares favorably with the frequent renal changes with streptomycin. There were no abnormal hematopoietic effects. Only one patient developed a severe vestibular disturbance; this is a great improvement. However, 3 patients developed changes in the cochlear branch of the eighth nerve which only became apparent one month after the drug had been stopped. This is much worse than the effect of streptomycin. Resistance studies, which were complete in only 12 cases, showed development of resistance in 5 cases.—*Dihydrostreptomycin in the treatment of pulmonary tuberculosis, S. T. Allison, R. Volk & G. R. Vitagliano, New England J. Med., July 14, 1949, 241: 52.—(A. G. Cohen)*

**Streptomycin for Tuberculosis.**—A series of 150 patients with various types of tuberculosis were treated with streptomycin, 1.0 to 3.0 Gm. daily. Virtually all patients with meningeal or miliary tuberculosis received 3.0 Gm. daily for four months. Of 12 patients treated for proved tuberculous meningitis, 9 died, a tenth is dying and 2 are well after more than one year. Of 13 patients treated for acute hematogenous tuberculosis, 8 are dead and 5 are alive. Four of the 5 survivors have been in complete remission for more than one year. Patients with pulmonary tuberculosis treated with streptomycin tend to follow one of three patterns: (*1*) The disappearance of symptoms with extensive roentgenologic clearing, cavity closure, and reversal of infectiousness was seen

only in predominantly exudative disease of relatively short duration; (*2*) a temporary improvement followed by relapse associated with drug-resistant organisms was observed in a minority of predominantly exudative infections but was frequent in chronic fibrocavernous disease; (*3*) roentgenographic clearing with cavity shrinkage which fell short of complete closure was the most frequent course during streptomycin. After temporary control of the progressive infection by drug therapy, it was possible to institute collapse therapy in these cases. In the present series the earliest detection of drug-resistant cultures was after 5 weeks of streptomycin; in general, resistance appeared within 60 to 90 days of therapy. One or two months of streptomycin therapy may be all that is necessary to attain a satisfactory result in predominantly exudative pulmonary tuberculosis with or without thin-walled cavities. Several months of streptomycin may be expected to result in permanent remissions in a small but impressive minority of patients with acute miliary tuberculosis or meningitis. In most patients with chronic pulmonary tuberculosis extensive resolution and natural repair are not possible. In these cases, streptomycin results in temporary improvement and the eventual emergence of drug-resistant infections. These patients may be significantly aided by intelligently timed antimicrobial therapy used in conjunction with surgery.—*Streptomycin in the treatment of tuberculosis, W. McDermott, J. Nat. M. A., July, 1949, 41: 167.—(L. Hyde)*

**Streptomycin and Promizole for Tuberculous Meningitis.**—Promizole is of no value in tuberculous meningitis but, of 7 cases of miliary tuberculosis in children treated with the drug, 5 survived without relapses or meningeal complications. The only complication is a goitrogenic action and the drug can be used safely for long periods of time. More recently, the superior action of streptomycin has become evident. It was decided to use the two drugs in combination, thus taking advantage of the more rapid action of streptomycin and of the more sustained action without toxicity of promizole. It is to be noted that 70 per cent of cases of tuberculous meningitis also show miliary dissemination. Ten cases of miliary tuberculosis in children were treated with a daily dose of 1.0 Gm. of streptomycin for 120 days. Promizole was given orally in sufficient dosage to yield blood levels of 1.0 to 3.0 mg. per 100 cc. This was maintained for three years. Eight of the 10 cases were alive and well four to twenty-one months after treatment was begun. There was a more rapid disappearance of the miliary mottling than with promizole alone and no meningitis developed in any case. Eighteen cases of tuberculous meningitis were treated. Ten have lived longer than six months; 5 are dead; none is crippled. Streptomycin was given intramuscularly in doses of 0.5 Gm. twice daily for 180 days. The drug also was given intrathecally in a dose of 0.1 Gm. daily until toxic symptoms or mechanical difficulties appeared. Then the dosage was reduced to 0.1 Gm. every other day, and, if necessary, to 0.05 Gm. every second or third day until an arbitrary total of 40 injections was given. Promizole was given orally every six hours. The initial daily total dose was 1.0 Gm. for several days. If no toxic symptoms appeared, the dose was increased by 1.0 to 2.0 Gm. daily every few days until blood levels of 1.0 to 3.0 mg. per 100 cc. were achieved. This was continued for three years. If the condition relapsed, the course of streptomycin was repeated. Promizole combined with streptomycin was found to be less toxic than promizole alone but streptomycin gave the usual toxic symptoms. There were great individual variations in the treatment and in the promizole levels in the blood and spinal fluid. The spinal fluid streptomycin levels decreased as the condition improved. The drug was not present after intramuscular injection if there was no meningitis and this fact was of diagnostic importance in cases of miliary tuberculosis under treatment. The cell count returned to normal by the end of the course of streptomycin treatment. The chloride determinations were not valuable and the sugar was normal in 4 early cases of meningitis. In the absence

of meningitis, the Levinson test was negative and the colloidal gold curve normal; these tests plus the streptomycin determination were of great diagnostic value. Usually, no response to treatment was apparent in meningitis cases until the second month, which may be due to the irritating effects of the drug, and improvement continued after the drug was stopped.—*Streptomycin and promizole in miliary tuberculosis and tuberculous meningitis in children, E. M. Lincoln & T. W. Kirmse, Lancet, May 7, 1949, 1: 767.*—*(A. G. Cohen)*

**Streptomycin in Pulmonary Resection.**—Up to 1944 less than 90 cases of pulmonary resection for tuberculosis had been reported in the literature. By January 1947 when streptomycin was first used in surgical cases in the sanitarium at Oteen, North Carolina, and at the Western North Carolina Sanatorium it was felt, however, that pre-streptomycin surgery was sufficiently standardized to serve for comparison. In the present series of cases, streptomycin was given one week before and two weeks after surgery; penicillin was instilled into the pleural cavity at operation and was given postoperatively. Of the 74 resections reported, 35 were lobectomies with one death and 39 were pneumonectomies with 5 deaths. In 25 per cent of the cases, particularly in resections after thoracoplasty, there was gross contamination of the pleural cavity by rupture of cavities, yet this accident produced no empyema or wound infection.—*An evaluation of streptomycin as a protective agent in pulmonary resection for tuberculosis, J. A. Moore, J. D. Murphy & P. D. Elrod, J. Thoracic Surg., February, 1949, 18: 45.*—*(R. E. MacQuigg)*

**Streptomycin and Resections.**—The results of resections for pulmonary tuberculosis were compared in 100 operations in which streptomycin was employed and in another 100 in which it was not used. The nonstreptomycin group represents an earlier period in the development of the surgical technique than does the streptomycin group. There were 27 surgical deaths among the cases not treated with the drug and 16 deaths in the streptomycin group. Operative spreads were reduced from 15 per cent in the first group to 1 per cent in the second. The authors believe that the mortality in resection for tuberculosis can now be set at some figure over 5 per cent, the risk depending largely on the type of case selected. —*Comparison of results in two hundred consecutive resections for pulmonary tuberculosis, C. P. Bailey, R. P. Glover & T. J. E. O'Neill, J. Thoracic Surg., February, 1949, 18: 36.*—*(R. E. MacQuigg)*

**PAS for Pulmonary Tuberculosis.**—The value of para-aminosalicylic acid (PAS) in the exudative type of pulmonary tuberculosis is becoming established. A series of 37 cases was treated on a dosage schedule of: 30 Gm. daily in divided doses on Monday and Tuesday, 20 Gm. daily on Wednesday through Saturday, no drug on Sunday. A blood level of 11 to 17 mg. per 100 cc. was thus achieved and maintained. The cases were all of the acute bilateral exudative type, either of recent origin or with recent spread. All had positive sputum and had been progressive for two to six months. The treatment was given for many months. In 31 cases there was a drop in temperature; in 35 there was a reduction in the amount of sputum. Cough diminished and the sense of well-being improved in every case. The sputum remained positive in 30 cases and was converted in 6. Radiographic improvement lagged behind clinical changes. There was nausea in 22 cases; frank hematuria of a transitory character appeared in 4 cases. The urine should be alkalinized while the drug is being used. The organisms did not develop resistance to the drug.—*Para-aminosalicylic acid (P.A.S.) in pulmonary tuberculosis, M. M. Nagley & M. H. Logg, Lancet, May 28, 1949, 1: 913.*—*(A. G. Cohen)*

**PAS for Tuberculosis.**—A series of 22 patients with advanced chronic pulmonary tuberculosis were treated with PAS, 10 to 11 Gm. daily in repeated courses of three weeks, with free intervals of one week. Clinical improvement took place in all instances, char-

acterized especially by reduction in cough and expectoration, decrease in fever, and improvement in well-being. These favorable effects generally were manifested within the first week of treatment. A favorable clinical response was noted also in patients whose organisms had become resistant to streptomycin. In a few patients recently treated by "lung immobilization" in the equalizing pressure chamber, PAS has been given in the hope of shortening the time required for cavity closure.—*The use of para-aminosalicylic acid in chronic pulmonary tuberculosis, C. Eastlake, Jr., & A. L. Barach, Dis. of Chest, July, 1949, 16: 1.*—(*E. A. Rouff*)

**Effect of Para-aminosalicylic Acid.**—The effect of para-aminosalicylic acid (PAS) upon the appearance of induced resistance of *M. tuberculosis* H37Rv to streptomycin was studied. All tests were performed in the sorbitan monooleate albumin medium of Dubos and Davis. The tubercle bacilli were resistant to 20,000 units of streptomycin per ml. after repeated exposure over a period of 80 days. When the test was repeated, the final inhibiting concentration was greater than 10,000 units per ml. after a total of 120 days of exposure. The streptomycin-resistant strain retained its sensitivity to PAS. Exposure of tubercle bacilli to PAS for a period of 120 days failed to produce an increase in their resistance to this agent. The addition of relatively low concentrations of PAS to streptomycin (approximately 0.5 γ to one unit) prevented or greatly retarded the *in vitro* development of streptomycin resistance. This compound at relatively low concentrations appears to offer promise as an agent to prevent *in vivo* the development of resistance to streptomycin by the tubercle bacillus. When used so as to maintain high concentrations, it may exert a therapeutic action in human tuberculosis when resistance to streptomycin already has developed.—*The in vitro effect of para-aminosalicylic acid (PAS) in preventing acquired resistance to streptomycin by Mycobacterium tuberculosis, O. E. Graessle & J. J. Pietrowski, J. Bact., April, 1949, 57: 459.*—(*F. G. Petrik*)

**Streptomycin Sensitivity.**—From October, 1947 to November, 1948, 14 tuberculosis patients were treated with streptomycin at a Rio de Janeiro sanatorium. Two of 3 nurses handling relatively large amounts of the drug showed a severe anaphylactic reaction. Symptoms included urticaria in unprotected parts of the body, ocular involvement with pruritus, discharge, and a burning sensation. The condition became so serious in one case that the nurse had to quit work for a while. Both patients recovered and sensitivity tests were positive. In 1948, 7 similar cases were reported from Argentina.—*A estreptomicina como causa de doença profissional, A. C. Alvim & E. A. do Nascimento, Clin. Tisiol., January-March, 1949, 4: 119.*—(*A. A. Moll*)

**Rabbit Eye Test.**—The antituberculous effectiveness of various substances can be tested *in vivo* by measuring their inhibitory effect against intracorneal inoculations in rabbits. A standardized dose of approximately 300 virulent bovine tubercle bacilli produces corneal lesions in the untreated eyes after a reasonably uniform latent period of twelve to fourteen days in one-half of the animals. injections of streptomycin or para-aminosalicylic acid into the vitreous were made in one infected eye, leaving the other eye as an Infected but untreated control. The drugs sometimes were injected a few hours after infection was established; in other cases, after lesions had already appeared; in others, before infection was produced. Both drugs were found to be effectively antituberculous by these methods.—*Intracorneal infection as a method for testing antituberculous substances, P. A. Gardner, R. J. W. Rees, & J. M. Robson, Brit. J. Pharmacol., June 1949, 4: 209.*—(*A. A. Cohen*)

**Streptomycin in the Pleural Cavity.**—Streptomycin was instilled into the chest cavities of dogs and the pleurae were removed seven days

later. No damage attributable to the drug was found. Absorption of the streptomycin was rapid from scarred as well as from unscarred pleurae.—*Experimental and clinical studies of the role of streptomycin in the pleural cavity, E. J. Beattie, Jr., B. Blades & C. Horton, J. Thoracic Surg., February, 1949, 18: 25.*—(*R. E. MacQuigg*)

**PAS in Bacterial Metabolism.**—The *in vitro* action of para-aminosalicylic acid (PAS) against tubercle bacilli is antagonized by para-aminobenzoic acid. At present it is only possible to say that tubercle bacilli apparently utilize para-aminobenzoic acid in such a fashion that insertion of a hydroxyl group in the molecule adjacent to the carboxylic group produces strongly inhibitory action on growth. The same substitution has little or no effect on other bacteria.—*Para-aminosalicylic acid in the metabolism of bacteria, W. C. Tobie & M. J. Jones, J. Bact., May, 1949, 57: 573.*—(*F. G. Petrik*)

**Usnic Acid Derivatives.**—The entire usnic acid molecule is involved in its action against tubercle bacilli since any major alteration in the molecule reduced or destroyed the activity. This is in marked contrast to the equal activity previously demonstrated for steroisomeric usnic acids. A total of 33 compounds, related to usnic acid, were tested for antibacterial activity against *M. tuberculosis* H37Rv.—*Antibacterial activity of d-usnic acid and related compounds on M. tuberculosis, A. Marshak, W. B. Schaeffer, & S. Rajagopalan, Proc. Soc. Exper. Biol. & Med., April, 1949, 70: 565.*—(*F. B. Seibert*)

**Tuberculostatic Effect of Subtilin.**—The effect of subtilin on the growth of the virulent, human type tubercle bacillus, H37Rv, was tested in 4 liquid media: Proskauer and Beck's synthetic medium; the Youmans and Karlson modification of Proskauer and Beck's medium; Proskauer and Beck's with 10 per cent beef serum; and the sorbitan monooleate albumin medium of Dubos and Middlebrook. The effect of subtilin on the course of tuberculosis in guinea pigs was also tested. Of 34 guinea pigs infected with *M. tuberculosis* H37Rv, 10 were kept as untreated controls and 24 were started on treatment with subtilin six days after infection. Seventy days after infection all surviving animals were sacrificed. Subtilin has only a very slight inhibitory effect on the growth of the H37Rv strain in fluid media without a dispersing agent. In the presence of sorbitan monooleate the drug is moderately effective. Subtilin did not influence the course of a tuberculous infection in guinea pigs produced by the H37Rv strain. The dosage used was close to the maximal tolerated dose for prolonged therapy with this preparation.—*The tuberculostatic effect of subtilin in vitro and in vivo, W. Steenken, Jr., & E. Wolinsky, J. Bact., April, 1949, 57: 453.*—(*F. G. Petrik*)

**Tuberculostatic Action of Chloromycetin.**—Chloromycetin was only moderately bacteriostatic for virulent human-type tubercle bacilli *in vitro* as compared with streptomycin or para-aminosalicylic acid (PAS). The growth of the majority of 19 human-type strains and one bovine strain was completely inhibited by between 6.25 and 12.5 γ or more of the drug in the presence of serum. The degree of bacteriostatic activity was not markedly affected by the number of tubercle bacilli present. The bacteriostatic activity of PAS or streptomycin was not enhanced by the addition of chloromycetin. When administered in the diet in concentrations of 0.5 and 0.25 per cent, chloromycetin was slightly effective in suppressing experimental tuberculosis in mice, but nor when given subcutaneously.—*Tuberculostatic action of chloromycetin in vitro and in vivo, G. P. Youmans, A. S. Youmans, & R. Osborne, Proc. Soc. Exper. Biol. & Med., April, 1948, 67: 426.*—(*F. B. Seibert*)

**Tuberculostasis with Nocardia Extracts.**—The results of treatment of tuberculous mice with a crude Nocardia extract were compared with those of mice similarly treated with streptomycin. White Swiss mice were inocu-

lated with 1.0 mg. of tubercle bacilli (H37Rv) and divided into 3 groups: untreated controls, mice injected twice daily with 1.5 mg. of streptomycin; and a group similarly injected with a crude extract of Nocardia. The survivors of each group were killed three to five weeks after inoculation. The results indicate that unpurified Nocardia extracts suppress the tuberculous process in mice treated twice daily with doses of 25 mg. Data obtained simultaneously from tuberculous mice treated with 1.5 mg. of streptomycin twice daily indicated a similar suppression of the tuberculous process. The toxicity of the unpurified Nocardia extracts at the dose levels used was found to be considerably greater than that of streptomycin. The tuberculostatic substance from Nocardia must be purified before a more precise evaluation can be made of the new antibiotic.—*The tuberculostatic action of Nocardia extracts in white mice, E. W. Emmart, R. E. Kissling & T. H. Stark, J. Bact., May, 1949, 57: 509.*—(*F. G. Petrik*)

**Aureomycin for Pulmonary Changes in Pancreatic Fibrosis.**—Pancreatic fibrosis (mucoviscidosis) is a disease of infants in which the primary defect is an essential alteration in the mucus-secreting glands. The lesions are not strictly confined to the pancreas, and other organs are involved in different degrees. Pulmonary complications are frequent early in the disease, often including a paroxysmal cough at times suggestive of pertussis. The respiratory rate is increased. There may be wheezing respirations and the production of thick tenacious sputum. Atelectasis and emphysema with infection are the chief roentgenographic features. The chest is often rounded with an increased anteroposterior diameter; the vital capacity and exercise tolerance are decreased. Clubbing of the fingers or toes and cyanosis may follow. Bronchiectasis and *Staphylococcus* abscesses may develop. The use of sulpha drugs, penicillin, and streptomycin is a great advance in the treatment of the disease. Aerosol penicillin and streptomycin alternating with oral sulphadiazine is now routine treatment and has proved very beneficial. However, aerosol treatment in infants is tedious and expensive. Since *Staphylococcus aureus* cultured from the sputum was found to be sensitive to aureomycin, this drug was tried in 35 cases. The daily dose was 20 to 30 mg. per Kg. in divided or single doses administered in food or drink. The flora of the nose and throat were not changed substantially after treatment but the *Staphylococci* did show increased resistance. There was rapid amelioration of the cough, dyspnea, and respiratory distress, with fall in the fever often within two to three days. The general condition improved. In infants, administration of over 500 mg. of the drug daily often gave a troublesome diarrhea. There was some improvement roentgenographically but not as great as clinically. All in all, good results were obtained in 31 of the 35 cases but discontinuance of the drug resulted in prompt reappearance of symptoms.—*Aureomycin therapy in the pulmonary involvement of pancreatic fibrosis (mucoviscidosis), H. Schwachman, A. C. Crocker, G. E. Foley & P. R. Patterson, New England J. Med., August 4, 1949, 241: 185.*—(*A. G. Cohen*)

**Penicillin and Antibody Response.**—This study was performed on a group of 127 army men in whom a definite diagnosis of hemolytic streptococcal pharyngitis was made. Three treatment schedules were followed in order to evaluate differences in streptolysin antibody response. In an untreated control group 84.3 per cent showed a rise in titre which averaged 462 units. In a group receiving 300,000 units of crystalline penicillin once a day for 7 days, 63.8 per cent showed an average rise in titre of 224 units. In the third group on conventional therapy of 20,000 to 50,000 units of penicillin every three hours for an average of 5.6 days, 13.8 per cent showed an average rise of titre of 162 units. Thus the degree of suppression of antistreptolysin formation was proportional to the duration of the antibacterial action of penicillin maintained during the 24-hour period.—*The comparative effects of continuous and intermittent penicillin therapy on the formation of antistreptolysin in hemolytic*

*streptococcal pharyngitis, E. Kilbourne & P. Loge, J. Clin. Investigation, July 1948, 27: 418.—(S. Hadley)*

## Laboratory Studies

**Nutrition in Experimental Tuberculosis.**—Wistar rats, which had lived for a number of generations on diets containing respectively 15, 25, and 40 per cent of protein, were inoculated with virulent bovine tubercle bacilli and the course of tuberculosis followed. The disease was less extensive and life was much longer in the rats on the 40 per cent protein diet than in the other 2 groups, and the degree of localization of the disease was better. The number of bacilli in lesions was smaller in the 40 per cent series, the extent of pneumonia was less, and there was less dissemination of tuberculous lesions. A characteristic feature of the long-lived animals was a progressive change in the cellular type of reaction from an early infiltration of mononuclears with little cytoplasm to a stage of consolidation with epithelioid cells and finally to a "regressive" type of mononuclear reaction in which lesions decreased in size, epithelioid cells were few, and mononuclears with little cytoplasm predominated.—*Experimental studies on nutrition in tuberculosis: The role of protein in resistance to tuberculosis, T. A. Koerner, H. R. Getz & E. R. Long, Proc. Soc. Exper. Biol. & Med., May, 1949, 71: 154.—(F. B. Seibert)*

**White Cell Lysis by Tuberculoprotein.**—In the tuberculous human, as well as in the guinea pig, the neutrophil leukocytes are specifically lysed when in contact *in vitro* with protein extracts of the tubercle bacillus. Although the lymphocytes from tuberculous mice, guinea pigs, and humans are specifically sensitive to tuberculoprotein, the neutrophil leukocytes are affected only in those species which show a positive delayed-type tuberculin skin test, i.e., in guinea pigs and humans. In the tuberculous mouse, which fails to develop delayed-type skin hypersensitivity reactions to tuberculoprotein, lympholysis occurs but other cell types remain unaffected. Complement seems to be necessary for the cytolysis.—*In vitro lysis of leukocytes from tuberculous humans by tuberculoprotein, P. Fremont-Smith & C. B. Favour, Proc. Soc. Exper. Biol. & Med., April, 1948, 67: 502.—(F. B. Seibert)*

**Plasma Factor for Lysis of Leukocytes.**—Cytolysis of human white blood cells by tuberculin occurs only in the presence of plasma from tuberculous subjects. White blood cells from healthy tuberculin-negative humans will undergo similar tuberculin cytolysis in the presence of such tuberculous plasma.—*A plasma factor responsible for in vitro lysis of leukocytes by tuberculoprotein, J. M. Miller, C. B. Favour, B. A. Wilson & M. A. Umbarger, Proc. Soc. Exper. Biol. & Med., April, 1949, 70: 738.—(F. B. Seibert)*

**Neohetramine in Experimental Tuberculosis.**—Young tuberculin-negative guinea pigs were infected with virulent tubercle bacilli (H37Rv); all reacted to 1.0 mg. of Old Tuberculin ten days after infection. A group of 20 animals received Neohetramine, 6 mg. subcutaneously twice daily; a like number served as controls. At no time did the treated guinea pigs show any change in reaction to tuberculin. The control guinea pigs developed a somewhat slowly progressive disease with moderate fibrosis and caseation. In the treated animals the disease was decidedly more chronic in character, the tubercles showing more fibrosis and lymphocytes being prominent in the lesions. Using a method of grading the lesions in various organs, it was demonstrated that the Neohetramine-treated group had approximately one-half as much gross tuberculosis as the controls. Neohetramine had no effect on tubercle bacilli *in vitro*. It was felt that this drug suppressed hypersensitivity reactions and might therefore be best suited for treatment of exudative tuberculosis in combination with streptomycin.—*Neohetramine in the treatment of experimental tuberculosis, C. J. Duca & J. V. Scudi, Ann. Allergy, May-June, 1949, 7: 318.—(B. Hyde)*

**Riboflavin and Growth of Tubercle Bacilli.**—A slightly virulent strain of *M. tuberculosis hominis* was cultured in a vitamin-free medium or in media to which riboflavin with or without other vitamins and biotin were added. The presence or absence of riboflavin made no difference in the growth of the tubercle bacilli but it slowly disappeared from the medium during the growth. Conversion to lumichrome was possible since crystals of the latter were found in the medium.—*Riboflavin and growth of tubercle bacilli, H. C. Hou, Proc. Soc. Exper. Biol. & Med., April, 1949, 70: 582.—(F. B. Seibert)*

**Dubos Medium with Penicillin.**—Of 300 clinical specimens, 134 were positive for tubercle bacilli on Dubos solid oleic acid-albumin medium containing 100 units per cc. of penicillin, but only 91 were positive on the Dubos medium without the penicillin to restrain contaminants. On a standard egg-potato medium 120 were positive. The Dubos medium was also considered superior because of the ease with which growth could be observed on the transparent agar and because of the characteristic cord-like appearance of virulent tubercle bacilli, not seen in the avirulent forms or other organisms.—*Evaluation of Dubos solid medium containing penicillin in the isolation of tubercle bacilli, J. W. Smith, J. Humiston, W. P. Cregar, & W. M. M. Kirby, Proc. Soc. Exper. Biol. & Med., April, 1949, 70: 589.—(F. B. Seibert)*

**Cultivation of M. tuberculosis.**—A comparison was made of the effect of treating sputum with hydrochloric acid and with trisodium phosphate in preparation for culture in Dubos-Davis and Petragnani media. A total of 245 sputum specimens were homogenized, equal portions were treated with hydrochloric acid and trisodium phosphate and cultured on Petragnani medium. Of 179 specimens from which growth was obtained, 150 yielded cultures from portions treated by both methods. Growth was obtained from only the acid-treated portion in 21 specimens and from only the phosphate-treated specimens in 8. The distorted appearance of the organisms in smear preparations from phosphate-treated sediments and from young cultures is evidence that this treatment adversely affects the organisms. The observations suggest that the use of trisodium phosphate tends to reduce the number of viable organisms and to affect adversely the surviving bacilli. Both Dubos-Davis fluid medium and Petragnani solid medium were effective in the cultivation of *Mycobacterium tuberculosis*. Acid-fast bacilli treated with trisodium phosphate appear to grow less readily on Petragnani medium than bacilli from the same specimens treated with hydrochloric acid. Some of these trisodium phosphate-treated specimens grew in fluid medium and not on solid medium which suggests that the fluid medium may be more satisfactory under these conditions. Because of technical difficulties in the preparation of Dubos-Davis fluid medium and in the preparation of stained smears from the growths in this medium, it would seem that there is little advantage in the wide scale adoption of this medium in public health laboratories.—*Cultivation of Mycobacterium tuberculosis. A comparison of hydrochloric acid and trisodium phosphate in the preparation of sputum and of fluid Dubos-Davis medium and Petragnani medium, M. Beattie, J. Lab. & Clin. Med., June, 1949, 34: 733.—(F. G. Petrik)*

**Collateral Intralobar Ventilation.**—In rabbits and dogs it is known that all parts of the pulmonary lobe communicate freely outside of the bronchi under normal respiratory conditions, probably by way of the alveolar stomata. It is now demonstrated that the same is true in man. When a lobar bronchus is obstructed atelectasis follows, but when a side bronchus is obstructed there usually is no collapse because of this collateral circulation of air. The collateral circulation, however, is eliminated by anatomic conditions such as secondary fissures, by inflammation, or shallow breathing.—*Collateral ventilation, P. Baarsma & M. Dirken, J. Thoracic Surg., April, 1948, 17: 238: Collateral ventilation in man, P.*

*Baarsma, M. Dirken & E. Huizinga, J. Thoracic Surg., April, 1948, 17: 252.—(R. E. MacQuigg)*

**Effect of Artificial Respiration on Circulation.**—Tracer substances such as radioactive sodium, fluorescein, and oxygen were injected into animals immediately after death by asphyxiation. Mechanical inflation and deflation of the lungs produced movement of blood over the entire body without any heart action. Thus oxygenated blood could be transported to brain or heart and medications might be transported to vital centers. Heparin is of value in such resuscitation. Mechanical resuscitators alternating positive and negative pressure were far more efficient in circulating blood than were machines employing positive or negative pressure alone.—*The effect of pulmonary inflation and deflation upon the circulation, S. Thompson, J. Thoracic Surg., June, 1948, 17: 323.—(R. E. MacQuigg)*

**Cardiac Output Studies.**—Almost simultaneous determinations of cardiac output according to the direct Fick (cardiac catheterization) and acetylene gas inhalation methods were made in 8 subjects in order to explain a well-known discrepancy existing between these methods. The Fick method gave values about 45 per cent lower than the Grollman acetylene gas rebreathing estimations. However the experimental error (coefficient of variation) for the Fick method was 5.6 per cent and for the acetylene method was 21 per cent. It was shown that the error in the latter results from the fact that significant amounts of acetylene appear in the pulmonary artery within ten to fifteen seconds after starting to breathe acetylene. Since it is impossible to get full mixing of the gas in this time these factors will always be inherent sources of error. Any method using the inhalation of foreign gas will give values for arteriovenous oxygen difference which are too large if the gas sampling is not completed before fifteen seconds after the start of rebreathing. The error will not be constant but will vary with the speed of circulation.—*A comparison of the direct Fick and the Grollman methods for determinations of the cardiac output in man, L. Werko, S. Berseus, & H. Lageröf, J. Clin. Investigation, May, 1949, 28: 516.—(S. Hadley)*

**New Congo Red Test.**—The authors present and justify a new, simplified, and accurate method of performing the Congo Red absorption test for amyloidosis. The inaccuracy of the initial two- to four-minute sample caused by early absorption and inadequate mixing of the dye is eliminated by computing a theoretical initial concentration. It was found that the blood volume for this calculation could be estimated from body weight or surface area as accurately as by extrapolation back to zero time from the ten- or thirty-minute samples. In addition this was shown to be better than estimating blood volume with Evans Blue dye which was demonstrated to be fixed by amyloid tissue. Since the greatest difference between the curves of the removal of Congo Red from the blood of amyloid and nonamyloid patients exists at 30 minutes, this was chosen as the time interval for the end point. By comparing values from 68 normal patients and 6 patients with clinical amyloid disease, 35 per cent of removal of the dye at 30 minutes is considered presumptive evidence of the disease. A Coleman Junior spectrophotometer was used in these determinations.—*A study of the disappearance of Congo Red from the blood of nonamyloid subjects and patients with amyloidosis, P. Unger, M. Zuckerbrod, G. Beck, & J. Steele, J. Clin. Investigation, January, 1948, 27: 111.—(S. Hadley)*

## Public Health and Epidemiology

**Tuberculosis in Bolivia.**—The history of tuberculosis in Bolivia embraces three periods. During the first the disease was considered almost nonexistent. Guilbert pointed out in 1862 that pulmonary tuberculosis was seen only in former seashore residents coming to the mountains to recover. The disease was uncommon in the Andean plateau and in 1884 the death rate, 600 per 100,000, was far below

that for Europe and most American countries. By 1901 the mortality had fallen to 100 to 150 per 100,000. As late as 1912 tuberculosis was comparatively rare. During the second period, beginning in the early twentieth century, the increasing incidence of tuberculosis attracted attention. Peruvian and Chilean newcomers were blamed for spreading the disease in La Paz. In this city the general death rate increased by less than 25 per cent in the period 1900–1915, but the tuberculosis mortality rose more than 650 per cent. By 1927 the attack rate among children was still low, but infection in adults was as common as in other South American countries. The mining area and the saltpeter works on the Pacific seemed to be the main centers of infection. Throughout the period the disease was increasing but its form seemed to be mild. The third period began with the Chaco War of 1932–1935, when tuberculous cervical nodes became prevalent among soldiers who also had mediastinal lesions. Reliable data from Upper Bolivia, and especially its six largest cities, show a sharp increase in the tuberculosis death rate which rose at La Paz, for instance, from 21 per 100,000 in 1900 to 130 in 1942. A roentgenographic survey in 1940 among 910 workers at La Paz showed 2 per cent of active tuberculosis and 43.6 per cent of arrested tuberculosis. The ratio of tuberculosis mortality to the general death rate has increased in the 1900–1942 period in La Paz from 0.5 to 9 per cent and at Sucre from 1.8 to 8.8 per cent, while it has decreased at Potosí from 7.4 per cent in 1910 to 3.6 per cent in 1943. Data for Lower Bolivia are poor but tuberculin surveys show a lower rate than in the Andean region. La Paz, the largest city, has the most contact with the outside world, the greatest population shifts and industrial development, and yet has a relatively low tuberculosis rate. On the other hand, the small town of Tarija has had an acute epidemic with a tuberculosis death rate averaging 372 per 100,000 for the period 1938–1942, after reaching an all time high of 1,549 per 100,000 in 1935 during the Chaco War.—*Esquema de la epidemiología de la tuberculosis en Bolivia, E. Vargas-Sivila, Clín. Tisiol., January-March, 1949, 4:* 9.—*(A. A. Moll)*

**Swiss Post-war Medical Summary.**—In the summer of 1945 a large scale plan of hospitalization for war victims from Austria, Belgium, France, Holland, Italy, and Luxemburg was formulated and put into effect with funds contributed to the Swiss Relief Organization. Subsequently, 3,650 tuberculous adult patients and 77 tuberculous children were hospitalized in various Swiss sanatoriums. A direct connection between the onset of illness and the effects of the war could be established in 64 per cent of the patients. Pneumothorax had been established in 1,085 (30 per cent) of the patients prior to admission and in 388 (10 per cent) after admission. Thoracoplasty was performed on 224 (6 per cent), paralysis of the phrenic nerve on 52 (one per cent). Streptomycin was administered to 127 patients. When discharged from the sanatoriums 2,888 patients had sputa negative for tubercle bacilli and 605 had sputa remaining positive for acid-fast bacilli. There were 141 deaths. The average duration of the cure was 331 days.—*Rapport Médical Final, Z. Makomaski, Schweiz. Ztschr. Tuberk., 1949, Supplementum.* —*(E. Dunner)*

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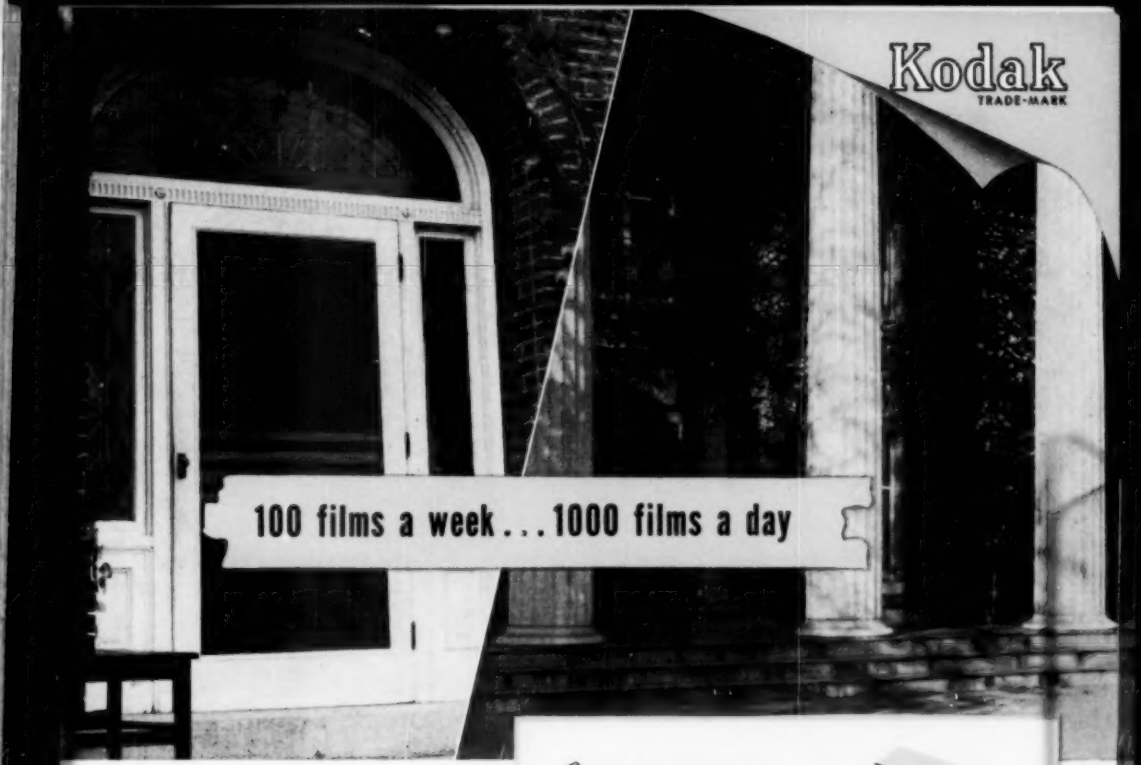


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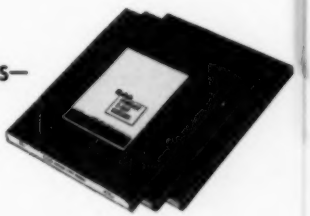

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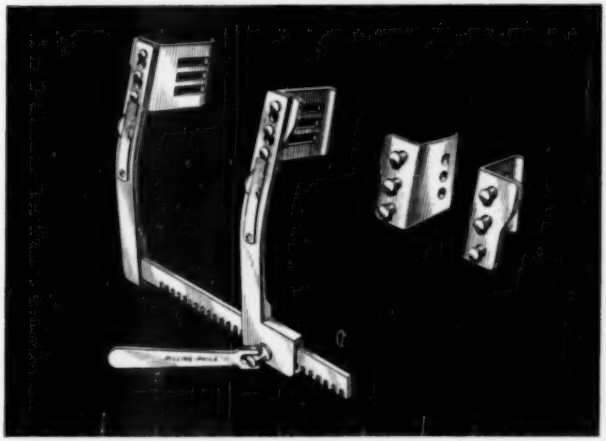

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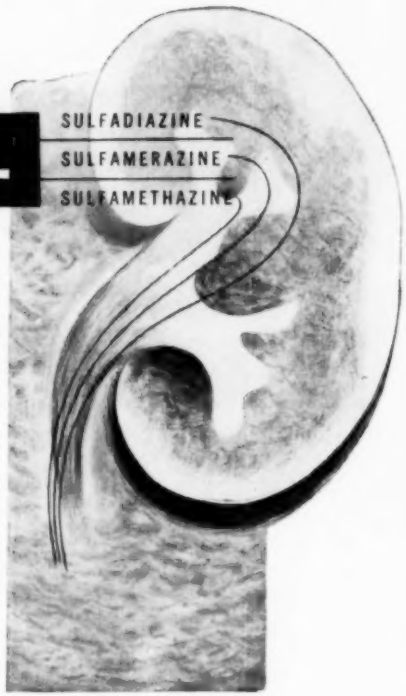


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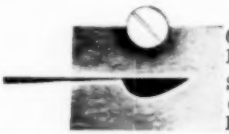

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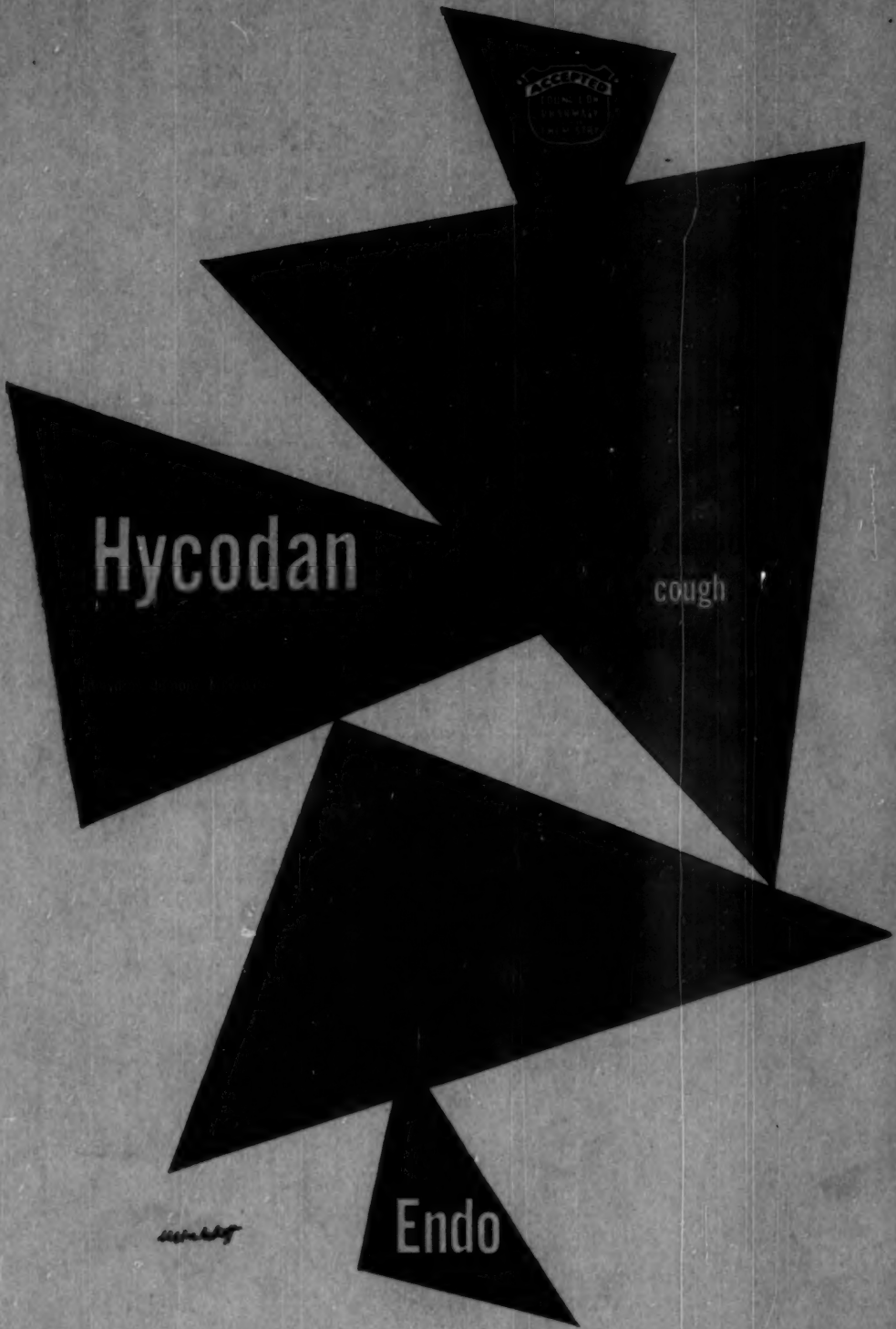
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